Diving and Hyperbaric Medicine

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Injuries during underwater rugby

Blood glucose measurement during HBOT

Outcomes after HBOT for intrauterine CO poisoning

Is HBOT safe in patients with left heart impairment?

Medication use in comorbid divers and diving fatalities

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A novel diving exposure suit

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PURPOSES OF THE SOCIETIES

To promote and facilitate the study of all aspects of underwater and hyperbaric medicine
To provide information on underwater and hyperbaric medicine
To publish a journal and to convene members of each Society annually at a scientific conference

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DIVING AND HYPERBARIC MEDICINE

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The Editor's offering

This issue of Diving and Hyperbaric Medicine is slightly smaller than several we have published over the COVID-19 pandemic and reflects a tailing-off in the surge in submissions that characterised the pandemic period. Submissions are currently tracking at a 'pre-pandemic' level and while this is associated with a degree of relief for the editorial team, we remain keen to see our societal members continue to submit high quality work to their own journal.

This is a topical issue for those whose focus is on hyperbaric medicine, with papers addressing three topics that might be considered controversial, or put another way, topics that are common subjects of discussion and uncertainty among hyperbaric practitioners.

First, the potential role of hyperbaric oxygen treatment (HBOT) in patients with COVID-19 pneumonia has been of significant recent interest to our community. The use of HBOT to improve oxygenation in hypoxic patients makes physiological sense, but whether this would be likely to alter the natural history of the disease and improve outcomes is not obvious. There are a number of theoretical arguments both for and against the possibility. Safety for patients and staff is also a concern. In this issue Dr Sylvain Boet and colleagues present a systematic review of relevant clinical evidence.[1] There is one non-randomised controlled study, and several case series or reports. Such data do not provide definitive answers to the burning questions, and the inevitable conclusion is that randomised studies are required. Nevertheless, the appraisal of relevant data provided by these authors constitutes a tempered and objective perspective that contrasts with occasional proselytizing for HBOT in various indications in the absence of adequate supporting studies. The field needs more of this sort of critical appraisal.

Second, this issue also contains an interesting report of fetal outcomes after HBOT treatment for carbon monoxide poisoning during pregnancy.[2] Even in jurisdictions where carbon monoxide poisoning has become a controversial indication for HBOT there remains a perception that symptomatic exposure to carbon monoxide during pregnancy remains a comparatively strong indication. However, there have always been concerns about theoretical hazards of HBOT exposure during fetal life. Dr Ozgok-Kangal presents the largest series (28 patients) to date with medium term outcome follow-up into infancy. His findings, though not definitive, are reassuring.

Third, another issue in hyperbaric medicine that occasionally provokes anxiety is the safety of HBOT for patients with impaired left ventricular function. This issue contains a paper by Dr Joëlle Vincent and colleagues describing tolerance of HBOT by 23 patients 40 years or older with a left ventricular ejection fraction equal to or less than 40%.[3] The outcomes were reassuring, though not universally so, suggesting that while treating heart failure patients with good indications for HBOT is reasonable, heightened vigilance with such patients is not misplaced.

Other interesting hyperbaric medicine papers discuss blood glucose monitoring during HBOT and the effect of HBOT on outcomes after breast reconstruction in irradiated tissue. Dr Carol Baines and colleagues have shown that capillary glucose (finger prick) sampling and a modern continuous glucose monitoring device (which essentially monitors interstitial fluid) were acceptably comparable with serum glucose measurements under hyperbaric conditions. Dr Eva Meier and colleagues showed that patients undergoing breast reconstruction after HBOT had a similar risk of post-operative complications compared to patients who did not receive HBOT but who had significantly less pre-operative radiation damage.

On the diving side, Dr Hans Lothar-Meyer and colleagues describe the epidemiology of underwater rugby injuries and provide this issue's cover photo taken by Konstantin Killer, a diver famous for photographing a somewhat different subject; mermaids, see https://www.unterwasser-model-kunstfotografie.de/. Simone Taylor and colleagues provide an interesting comparison of medication use between active comorbid divers and snorkelling and scuba diving fatality victims. Aaron Demers and colleagues describe the proof-of-concept for a wetsuit of novel design and material that may enhance thermal protection without compromising comfort or movement. There are two case reports: one that localises the anatomic source of haemoptysis in pulmonary barotrauma in two breath-hold divers; and the other describing an episode of iatrogenic arterial gas embolism during lumbar spine surgery in the prone position.

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Simon Mitchell, Editor

Cover photo:
Underwater rugby action. Photographer Konstantin Killer.

Original articles

Comparison of venous, capillary and interstitial blood glucose data measured during hyperbaric oxygen treatment from patients with diabetes mellitus

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Key words
Blood sugar level; Endocrinology; Hyperbaric medicine; Hyperbaric research; Patient monitoring

Abstract
(Baines C, Vicendese D, Cooper PD, McGuiness W, Miller C. Comparison of venous, capillary and interstitial blood glucose data measured during hyperbaric oxygen treatment from patients with diabetes mellitus. Diving and Hyperbaric Medicine. 2021 September 30;51(3):240–247 . doi: 10.28920/dhm51.3.240-247. PMID: 34547774.)
Introduction: Patients undergoing hyperbaric oxygen treatments (HBOT) have been shown to experience a reduction in blood glucose (BG) levels during a treatment. This necessitates frequent assessment of BG levels. Continuous glucose monitoring (CGM) may represent an alternative to the current finger prick monitoring method in-chamber, however, continuous sensor glucose (SG) data has not been validated *in situ*. The aim was to determine the validity of continuous SG and intermittent BG monitoring with serum BG levels in diabetic patients during HBOT.
Methods: Measurements were obtained (finger prick [capillary sample], CGM [interstitial fluid], and serum [venous sample]) at baseline, and at 30, 60, 90 and 120 minutes during the hyperbaric treatment. Data were analysed by calculating intraclass correlation coefficients (ICC) and using mixed effects linear regression.
Results: The ICC results (n = 10 patients) between the three methods indicated very high and statistically significant absolute agreement at baseline (pre-dive) (ICC = 0.90, 95% CI 0.74–0.97), at 30 minutes (ICC = 0.85, 95% CI 0.61–0.96), 60 minutes (ICC = 0.86, 95% CI 0.58–0.96), 90 minutes (ICC = 0.87, 96% CI 0.63–0.96) and 120 minutes (ICC = 0.90, 95% CI 0.70–0.97). Capillary glucose and CGM SG readings were each within 1 mmol·L^{-1} on average of the serum glucose reading, with multi-level linear regression finding the average difference between the CGM SG and capillary glucose methods of BG sampling was not statistically significant (P = 0.81).
Conclusions: The CGM SG data were comparable with glucose readings from capillary monitoring. Both CGM and capillary data were consistent with serum values.

Introduction

In Australia, there are 1.2 million people who are known to have diabetes, with an estimated 500,000 living with undiagnosed diabetes.[1] People living with diabetes are at risk of long-term secondary complications especially micro- and macrovascular complications that predispose them to an increased risk of skin ulceration and subsequent limb amputations.[2] For the group of patients that have diabetes and a wound, one therapeutic modality prescribed regularly is hyperbaric oxygen treatment (HBOT). HBOT is the administration of 100% oxygen in a pressurised environment,[3] and has been demonstrated to increase tissue oxygenation, cause vasoconstriction, fibroblast activation, down-regulation of inflammatory cytokines, up-regulation of growth factors, have antibacterial effects, potentiate antibiotics and produce a reduction in leukocyte chemotaxis.[4–6] Evidence from clinical trials further support this data.[7,8]

There is, however, a documented inconsistent and unpredictable impact on glucose levels in patients with diabetes during HBOT. One study reported that there was an average drop of '2.8 mmol·L^{-1} in 25 insulin dependent patients' under hyperbaric conditions.[9] The unpredictability of hypoglycaemic events during hyperbaric treatment impacts on the patient in several areas, including feelings of additional apprehension and stressfulness. There is evidence

cited elsewhere[10] of patients artificially raising their blood glucose and broadly adjusting their own diabetes medication to avoid a hyperbaric treatment related hypoglycaemic event.

Monitoring blood glucose (BG) levels in patients with diabetes during HBOT is essential as it provides reassurance to the patient and is a clinical reference for ongoing medical management. Usual BG monitoring includes intermittent testing with a lancet, a test-strip and a glucometer (point-of-care/finger prick monitoring) prior, during and often after the patient's routine two-hour daily HBOT. Given that most HBOT programmes require daily treatments for several weeks, repeated finger prick testing, in addition to usual BG level monitoring, can be onerous for both the patient and medical team.

An alternative to finger prick testing is a continuous glucose monitor (CGM). The CGM measures glucose from the patient's interstitial fluid and provides sensitive glucose trend data which is then applied to a patient-specific predictive algorithm.[11] Improvements in CGM technology over the last 10 years, the growing evidence for its clinical efficacy and recent supportive funding initiatives have resulted in increased usage of this monitoring modality in the clinical arena. Some authors suggest CGM allows for a much-improved chance of metabolic glucose control thus lessening the chances of hypoglycaemic events.[12–14]

Recent studies have reached a consensus on the use of the CGM for recreational divers.[15–19] There is agreement that CGM reduces risk but cannot currently be used while diving.[20] However, the use of the CGM to predict glucose trends during HBOT has not been thoroughly examined. There is a need to bolster the existing body of knowledge regarding CGM accuracy, reliability and safety when used in HBOT conditions in the diabetic population, prior to considering a change in clinical practice. The aim of this study was to examine the degree of agreement between continuous sensor glucose (SG) and intermittent capillary BG monitoring with serum BG levels under hyperbaric conditions in patients with diabetes.

Methods

This study was approved by the University of Tasmania, Human Research Ethics Committee (HREC) (H0015975).

An observational study was conducted to compare blood glucose levels ($mmol \cdot L^{-1}$) obtained from three simultaneous sampling points throughout a hyperbaric oxygen treatment among patients with diabetes. The three sampling methods included:

i Intermittent (finger prick) blood glucose (point-of-care monitoring);
ii Continuous glucose monitoring (CGM) measures of interstitial fluid glucose;
iii Serum blood glucose levels.

The study was undertaken in the Department of Diving and Hyperbaric Medicine (DDHM) at the Royal Hobart Hospital, Tasmania, Australia. The DDHM provided approximately 17,191 treatments delivered to 915 patients between 2010–2020.

The study group was drawn from patients receiving HBOT at the DDHM. The study eligibility criteria included adults (≥ 18 years), who were living with diabetes (type 1 or type 2), and who were deemed medically suitable to undergo HBOT in a multi-place hyperbaric chamber. All non-consenting adults, children or young people (< 18 years), and pregnant women were excluded from the study. A sample size of 29 participants was required assuming a correlation coefficient of 0.5, $\alpha = 0.05$, and $\beta = 0.2$. To accommodate the potential for 20% attrition or missing data, a sample target of $n = 35$ was pursued. Patients attending the service for medical assessment to ascertain their suitability for hyperbaric treatment, were screened for eligibility.

Venous serum samples were processed on site at the hospital laboratory using the hexokinase enzymatic reference method with the GLUC3 kit of the Cobas 6000 laboratory analyzer's c501 module (Roche Diagnostics, Rotkreuz, Switzerland), accredited by National Association of Testing Authorities (NATA), Australia.

The venous serum samples were drawn from each participant by a registered nurse (RN) into a blood collection tube containing sodium fluoride, a glycolysis inhibitor, used to limit the ex vivo consumption of glucose.[21] To minimise the effect on glycolysis of known variables, such as temperature and white blood cell count,[22] lapsed time from collection-to-separation of the blood sample did not exceed the test site's laboratory recommendation.

Capillary samples were obtained via the finger prick method and analysed on-site in the hyperbaric chamber using the FreeStyle Optium™ Neo glucometer (Abbott Healthcare, Massachusetts, USA). This glucometer measures glucose capillary whole-blood samples ($mmol \cdot L^{-1}$). Calibration is completed manually and all glucose measurements are performed using a glucose dehydrogenase (GDH) test strip as per the manufacturer's instructions. GDH test strips are the preferred electrochemical glucose measurement method as this counteracts the interference of oxygen in the blood sample, which in turn makes them more suited to the hyperbaric oxygen environment. The FreeStyle Optium™ Neo has been tested in the hyperbaric environment and found to be consistently accurate.[23]

A Minimed™ Medtronic Guardian™ Connect CGM device (Medtronic, Minneapolis, USA) was used in this study. The CGM provided a constant digital display of interstitial SG ($mmol \cdot L^{-1}$) that was refreshed every six minutes, a process grounded in a 'learned' predictive algorithm.[11,24] It involves an internal electronic calculation delivered via a predicted time lag.[25,26] The CGM sensor (TGA number 172028)

attached to the CGM transmitter (TGA number 138452) was worn by the participant during HBOT. The digital display of the CGM was via an app on a smart device (iPod). The iPod remained on the outside of the hyperbaric chamber during treatment. The Minimed™ Medtronic Guardian™ Connect CGM requires calibration against a capillary glucose every 12 hours. Calibration was performed as per the manufacturer's guidelines, using the same glucometer at all times.

Additional information collected at the time of sampling included date of birth, type of diabetes, diet (that day), current diabetes medication management, and any adverse event occurring in the hyperbaric chamber that resulted in additional medical treatment to the participant.

PROCEDURE

Insertion of the CGM into the participant occurred on day one of HBOT. Data collection for the study commenced on day two of their HBOT to allow for the sensor to be sufficiently 'warmed' but not 'bio fouled'.[27] The participant presented to the DDHM for routine hyperbaric treatment with the CGM in situ. The CGM site was inspected for any signs of infection and was calibrated using a finger prick glucose value obtained using the participant-specific allocated glucometer. A venous access cannula was placed in the participant's antecubital fossa vein by a medical practitioner using the research site's approved method. The in-situ venous cannula was accessed to draw serum samples.

Prior to the commencement of HBOT, baseline (time point 0 [T0]) blood glucose measures were obtained, including serum values, a finger prick value and the CGM-displayed sensor glucose value. During the two-hour HBOT, serum and finger prick sampling along with CGM sensor glucose reading interrogation was repeated at 30-minute intervals throughout the treatment – a total of four repeated sampling points (30, 60, 90 and 120 minutes being T1, T2, T3, T4 respectively). At completion of HBOT, the venous access cannula was removed, and the patient monitored for 30 minutes as a clinical precaution prior to discharge home.

DATA ANALYSIS

Absolute agreement between the three methods was assessed for each of the five monitoring time points. This was done by calculating an intraclass correlation coefficient (ICC) and its 95% confidence interval (CI) for each time point, using a multilevel linear regression with a random intercept for patients. The first ICC, termed 'intraclass correlation coefficient – absolute agreement' (ICC_{AA}), was defined as:

$$\frac{\text{variability (individual differences) between patients}}{\text{variability (individual differences) between patients + variability of the methods within a patient + random error}}$$

The test/retest or reliability of the three methods was assessed by calculating a second ICC and its 95% CI using a second multilevel linear regression with a random intercept for patients and for methods. This was based on pooling the data over the five time points. The second ICC, termed "*intraclass correlation coefficient – reliability/re-test*" (ICC_{RR}), was defined as:

$$\frac{\text{variability (individual differences) between patients + variability of the methods within a patient}}{\text{variability (individual differences) between patients + variability of the methods within a patient + random error}}$$

The ICC_{RR} assessed the correlation between measurements on the same subject with the same method. This model also allowed for patients' individual glucose responses while they were in the hyperbaric chamber by allowing each patient a random coefficient for time. Further, there was no assumption that each method had the same mean for its glucose measurements and hence a fixed term for method was entered into the regression. In other words, this model was a mixed effects model.[28]

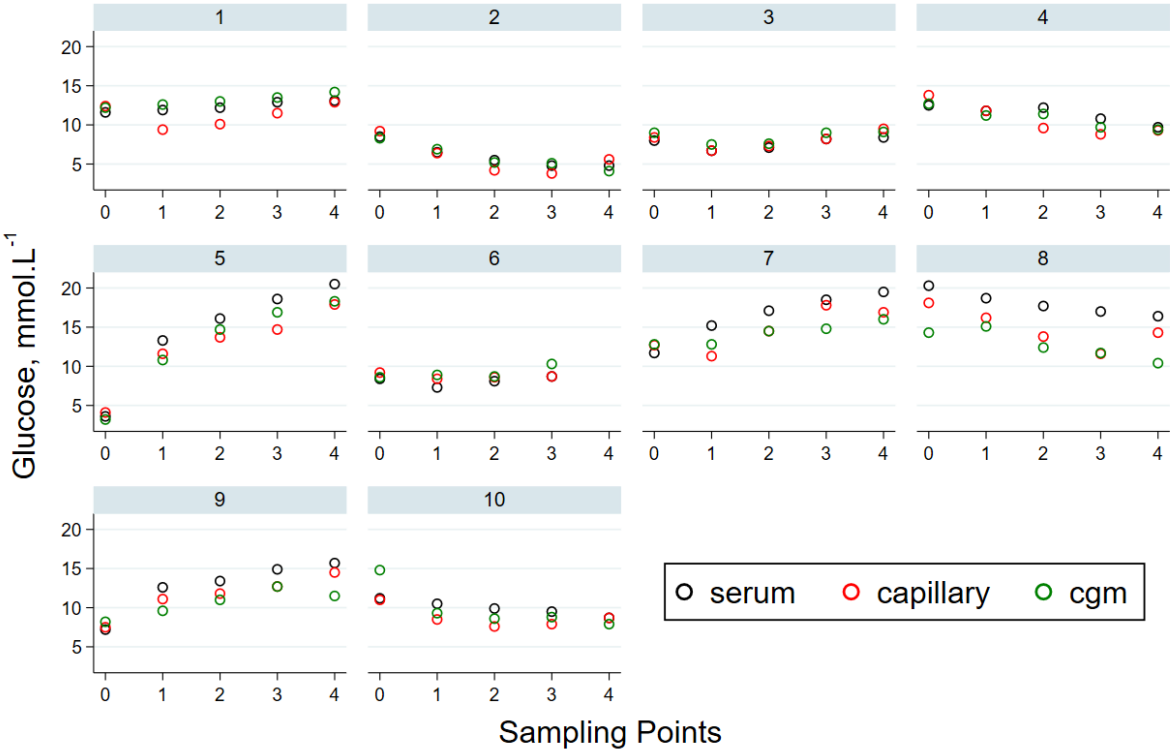
A third model, also mixed effects, was developed to use CGM SG readings to predict serum glucose readings. This is referred to as the recalibration model and was also based on a random intercept for each individual along with random coefficients for time. Glucose was modelled as a fixed effect in order to predict corresponding serum levels. Agreement between serum readings and the recalibrated CGM readings was assessed with a Bland-Altman plot.[29] Calculation of the ICCs, the mixed effects modelling, and generation of the Bland-Altman plot were done with Stata statistical software.[30]

Accuracy of the CGM is often validated using an accuracy metric termed the mean average relative difference (MARD). MARD is the mean of the sum of the differences between reference and sensor glucose values divided by the number of data points. A small MARD indicates that the CGM SG readings are close to the reference glucose value, whereas a larger MARD indicates greater discrepancies between the CGM SG and reference glucose values.[27,31] The MARD for blood samples were assessed. Statistical significance was set at $P < 0.05$.

Results

The study recruited 10 participants: nine males and one female. A sample size of $n = 35$ was intended but due to the lengthy recruitment phase, acceptance of a smaller number was necessary to progress the project. Participants were aged between 52–81 years of age. Two participants were classified as type 1 diabetes mellitus, one participant type 1 diabetes mellitus - latent autoimmune diabetes in adults (LADA), and seven were classified as type 2 diabetes mellitus who were either on insulin or oral hypoglycaemic medicines.

Figure 1
Participant glucose readings (mmol·L^{-1}) from serum, capillary and continuous glucose monitor (CGM) sampling at baseline (point 0) and the four subsequent sampling points at 30-minute intervals (points 1–4 on the Y axis) during HBOT



Glucose levels were obtained from the 10 participants from three separate measurements (capillary, interstitial CGM [SG], and serum) over the five time points during HBOT and are presented in Figure 1. Measurements for patient six at the 120-minute point were not taken due to the venous access cannula blocking. Measurements at each time point with the three methods indicate high similarity within each individual at any given time point. Over time, the three measurements for each participant track each other closely and there are no sudden reversals or changes in direction in glucose trend. Patients' glucose levels tracked differently for each patient. Some patients' glucose levels tended to rise, e.g., patients five and seven, others tended to decrease, e.g., patients four and ten, while some patients' trajectories were flat, e.g., patients one and three. The heterogeneity of patient trajectories was the reason for allowing each patient a random coefficient for time within the second and third multilevel model.

The results of the second model (mixed effects) are displayed in Table 2. Capillary glucose and CGM SG readings were each within about 1 mmol·L^{-1} on average of the serum glucose reading. The average difference of approximately 0.11 between capillary glucose and CGM SG readings were not statistically significant, $P = 0.81$. This model indicated that, across all time points, the three methods were in very close agreement with each other, ICC_{AA} 0.88, 95% CI

Table 1
Intraclass correlation coefficient – absolute agreement (ICC_{AA}) with 95% CIs for each glucose sample time; CI – confidence interval

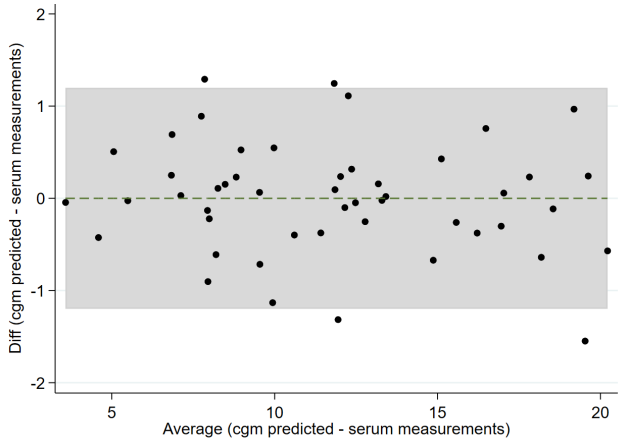
Sample	ICC_{AA} (95% CI)	*P*-value
Pre	0.90 (0.74–0.97)	< 0.0005
30 min	0.85 (0.61–0.96)	< 0.0005
60 min	0.86 (0.58–0.96)	< 0.0005
90 min	0.87 (0.63–0.96)	< 0.0005
120 min	0.90 (0.70–0.97)	< 0.0005

Table 2
Comparison of sampling methods across all time points.; * – denotes comparison with serum levels; CI – confidence interval; ICC_{AA} – Intraclass correlation coefficient – absolute agreement; ICC_{RR} – Intraclass correlation coefficient – reliability/retest

Variable	Estimate	95% CI	*P*-value
Fixed effects			
Constant	11.15	(8.84–13.47)	< 0.0005
Capillary*	-1.06	(-1.94–0.17)	0.019
CGM*	-0.95	(-1.84–0.07)	0.035
ICC			
ICC_{AA}	0.88	(0.72–0.96)	< 0.0005
ICC_{RR}	0.94	(0.86–0.98)	

Figure 2

Bland-Altman plot for the agreement between serum and recalibrated continuous glucose monitoring (CGM) (mmol·L^{-1})



0.72–0.96. The three methods' reliability (test/retest) was high, ICC_{RR} 0.94, 95%CI 0.86–0.98.

The results of the third model (mixed effects) which recalibrated CGM measurements to serum measurements are displayed in the Bland-Altman plot in Figure 2. The average difference between the calibrated and actual serum measurements was 0 with 95% limits of agreement of (1.2). This indicates that, based on this study's data, the recalibrated measurements were not biased and that 95% of recalibrated CGM measurements will be within (1.2) of serum measurements.

Mean average relative differences (MARDs) were generated, and the similarity of the CGM and capillary relative to serum were confirmed first using a repeated measures one-way analysis of variance (ANOVA) for each time point. A statistically significant effect was found for time for the mean capillary values [Wilks Lambda = 0.065, F (4,5) = 17.889, P < 0.01]. The multivariate partial eta squared result was 0.935, suggesting a moderate to large effect as per Cohen's classification.[32] *Post hoc* tests were examined to determine between which time points the differences were statistically significant. Mean capillary results pre-HBOT (T0) differ from subsequent readings at 30, 60, and 90 minutes (P < 0.05 in all cases), but do not differ from the 120-minute measurement (P = 1.000). Differences in CGM values across the time points were not statistically significant [Wilks Lambda = 0.487, F (4,5) = 0.1.315, P = 0.378]. The influence of time point was further examined by conducting repeated measures ANOVA using the mean capillary results as well as the serum values. MARD values are presented in Table 3.

Table 3

Mean average relative difference (MARD) values between finger prick and continuous glucose monitor (CGM) readings at different time points; Note: n = 10 except for Time 4 where n = 9. CI – confidence interval; IQR – interquartile range; Min–Max – minimum–maximum; SD – standard deviation

MARD	Finger prick	CGM
Time 0: pre-HBOT		
Mean (SD)	-5.40 (7.08)	-3.40 (16.30)
Median (IQR)	-7.56 (7.06)	-3.77 (17.39)
Min–Max	-13.89–10.84	-32.14–29.56
95% CI	-10.46–0.33	-15.06–8.25
Time 1: 30 min		
Mean (SD)	9.02 (12.29)	4.82 (15.48)
Median (IQR)	12.34 (19.54)	8.25 (26.51)
Min–Max	-15.07–25.66	-21.92–23.81
95% CI	0.22–17.82	-6.25–15.90
Time 2: 60 min		
Mean (SD)	14.04 (10.55)	7.58(12.20)
Median (IQR)	16.20 (14.08)	7.62 (22.56)
Min–Max	-6.17–23.64	-7.41–29.94
95% CI	6.49–21.59	-1.14–16.32
Time 3: 90 min		
Mean (SD)	13.83 (10.25)	5.3 (15.04)
Median (IQR)	15.80 (18.03)	8.25 (23.20)
Min–Max	0.00–31.76	-18.39–31.18
95% CI	6.49–21.16	-5.40–16.12
Time 4: 120 min		
Mean (SD)	2.48 (11.03)	11.35 (14.91)
Median (IQR)	4.12 (19.29)	10.73 (24.97)
Min–Max	-16.67–13.33	-8.40–36.59
95% CI	-5.99–10.96	-0.11–22.81

Discussion

The aim of this study was to investigate the use of the CGM under hyperbaric pressure. To achieve this, repeated glucose sampling measures using different techniques at pre-set time points were undertaken throughout a standard hyperbaric chamber treatment. At each time point (baseline, 30 minutes, 60 minutes, 90 minutes, and post-treatment), serum blood (via venous canula), capillary blood (via a finger prick) and CGM (via trend interstitial fluid) data were sampled. The results suggest that the three methods of measuring blood glucose yielded values that were statistically and clinically comparable before as well as during HBOT.

These results build on several studies published over the last decade that have examined the accuracy, reliability and functional properties of a CGM device when exposed to conditions associated with recreational diving or HBOT.[15–18,33] Early work identified the CGM as beneficial to the recreational diver as an accurate means of detecting hypoglycaemic episodes.[15] Others investigated the use of CGM in young, fit, recreational divers[17] and reported issues with the CGM housing and consequently device flooding. However, the CGM was accurate in detecting hypoglycaemic events. Although obtaining paired values (for example matching serum to CGM value) were impossible to obtain in a diving situation, it has been observed that the CGM detected significant numbers of hypoglycaemic events and can be used with confidence in diving situations.[16]

In an investigation of the "*Enlite*" sensor using *in vitro* methodology,[33] 16 sensors (n = 8 connected to iPro and n = 8 connected to Guardian REAL-Time) were exposed to hypobaric and hyperbaric conditions and different glucose concentrations. The sensors provided a constant stream of data during testing and no significant difference was seen in the hyperbaric conditions. In contrast, hypobaric conditions affected results in the low and high concentrations of glucose. The authors concluded that the general stability and level of accuracy that the CGM offers would support its use in both the hypobaric and hyperbaric environment. Finally, a small pilot study was undertaken using the Dexcom CGM and two diabetic participants involved in recreational diving.[18] Despite variations in how data were obtained and acknowledgement of excursions of acceptability according to the IOS standard, the authors recommended that diabetics continue to use CGM in recreational diving. The continuous glucose monitor offers an important alternative to intermittent BG monitoring via glucometer.

In addition to contrasting the three methods of glucose sampling, this study provided data about individual BG levels during HBOT. Glucose levels changed over the course of a single hyperbaric treatment. The change in glucose levels recorded by the three methods (venepuncture, finger prick, CGM) varied over time between participants, demonstrating that although some participants had a similar diagnosed physiology to their chronic diabetes, their glucose response varied. It was postulated that this was linked to their diet on the treatment day and consequently the metabolism of the carbohydrate load. All participants had a close alignment of their glucose readings by the three methods with a clear directional trend in their individual glucose data.

While the modelling was based on a small data set with repeated measurements, the recalibration results show the CGM may be a useful method compared to sampling serum and hence potentially interchangeable. It would be possible, after further validation, to incorporate recalibration with serum levels as part of the patient specific predictive algorithm. This is noteworthy, given that venous sampling is not usual practice during HBOT due to the invasive and time-consuming nature of the method.

It has been demonstrated that capillary (finger prick) sampling is considered painful, intrusive and burdensome by patients.[34] Evidence indicates that patients are supported by the CGM system and its ability to provide predictive trend data.[35] These findings facilitated management decisions that consequently reduced the rate of hypoglycaemia.[17] Given the heightened glucose testing that applies in a HBOT environment, the opportunity to integrate CGM SG readings to aid BG level monitoring and management, whilst minimising the impost to patients should be further explored. A larger study would be required of non-repeated measurements to verify the utility of this monitoring system. The ability to monitor BGL continuously whilst diving underwater or in a hyperbaric chamber has progressed and the development of the CGM has created greater and safer opportunities for divers and patients. Healthcare clinicians must recognise there are physiological differences between the glucose concentration in blood sources from veins, capillaries, arteries and interstitial fluid.[36] There is a need to bolster the existing body of knowledge regarding CGM accuracy, reliability and safety when used in HBOT conditions. Studies have reached consensus in the use of the CGM for recreational divers but the use of the CGM to predict glucose trends during HBOT is not yet fully established.

Although the introduction of a CGM for patients with diabetes undergoing HBOT is conceivably best practice, this would not make the glucometer/strip combination redundant. There will be instances where a short course of HBOT is prescribed and one-off blood glucose monitoring will be necessary. A glucometer would suffice in this situation. To date, a glucometer is necessary to assist in the calibration process of the CGM, however, future modelling of the CGM will explore the removal of this requirement. The use of the CGM will be patient- and treatment-course specific and as such there will be an ongoing role for both types of glucose monitoring equipment.

A limitation of the study is the small number of participants that were recruited. To assess the general utility of CGM SG readings as a good predictor of serum levels of glucose, further testing on a larger number of patients is required. It would not, however, be necessary to perform serial glucose measurements which have added unnecessary statistical burden.

Conclusion

CGM provides a real-time glucose trend that allows interventional treatment to be instigated at appropriate times, thus proactively managing hypoglycaemic situations as they eventuate in hyperbaric conditions. The CGM SG measurements were as accurate as those provided by a venous serum or finger prick glucose test. With routine use in the hyperbaric environment, the CGM device will likely prove to be a method of glucose monitoring that can be trusted by both clinicians and patients.

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Long-term infant outcomes after hyperbaric oxygen treatment for acute carbon monoxide poisoning during pregnancy

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Key words
Fetal development; Hyperbaric medicine; Long-term adverse effects; Pregnancy outcome; Pregnancy trimesters

Abstract
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Introduction: Carbon monoxide (CO) poisoning in pregnant women is linked to foetal mortality of 36–67%. This study assessed long-term fetal outcomes following hyperbaric oxygen treatment (HBOT) for acute CO poisoning in pregnant women. The effects of clinical severity parameters and pregnancy trimester were also analysed.
Methods: A retrospective review of 28 pregnant patients who received HBOT for acute CO poisoning between January 2013–June 2016 was made. Adverse events, birth week, birth weight-height, birth complications, and the age of crawling, walking independently, talking (first words) of their children were recorded.
Results: Twenty-eight singleton pregnancies were included. One fetus was dead before HBOT. Three adverse events were reported: abortion, premature birth, and limb malformation. All remaining patients (n = 24) delivered healthy term infants and reported normal neurophysiological development. At final interview the median age of babies was 34 (8–44) months and none had any diagnosed disease. There was no relationship between clinical severity parameters and long-term outcomes. However, the pregnancy trimester at the time of CO poisoning had a significant relationship to birth weight (P = 0.029). Also, the week of pregnancy at the time of the incident correlated with the age of walking independently (P = 0.043, r = 0.436).
Conclusions: This is the largest relevant series and longest follow-up to date. Adverse outcomes were likely incidental because the mothers' medical histories revealed alternative aetiologies. There was no definite evidence of fetal morbidity or mortality after HBOT in this study. HBOT may improve long-term fetal outcomes after in-utero CO poisoning without complications.

Introduction

Carbon monoxide (CO) poisoning is responsible for more than 20,000 emergency department (ED) admissions annually in the USA.[1] Pregnant patients are estimated to make up 4.6% to 8.5% of these cases.[2,3] Unfortunately, the resulting fetal mortality rate is between 36% and 67%, while the maternal mortality rate is between 19% and 24%.[4,5] Even for experienced practitioners, CO poisoning can be misdiagnosed easily due to its non-specific symptoms, which may lead to improper treatment and increase the degree of fetal morbidity and mortality.

The fetus is particularly susceptible to CO poisoning. Firstly, fetal haemoglobin has higher affinity for CO compared to maternal haemoglobin. Secondly, fetuses have a more prolonged CO elimination period than adults since they cannot increase their tidal volume or ventilation rate.[6] Outcomes resulting from CO poisoning depend upon the stages of gestation during poisoning, the severity of maternal CO exposure and the chronicity of exposure.[7,8] While exposure earlier in gestation might result in anatomical malformation, later exposures are expected to be related to neurological sequelae due to hypoxia.[7] Preterm delivery, hypoxic-ischaemic encephalopathy, hypotonia, cerebral palsy, areflexia, persistent seizures, microcephaly, cardiomegaly, limb malformations, fetal growth retardation, intrauterine fetal death, and even sudden infant death are reported to be associated with CO poisoning.[6,7]

Initial treatment for CO poisoning includes normobaric oxygen treatment (NBOT);[7,8] the effectiveness of NBOT for an affected fetus is difficult to ascertain as there is no diagnostic method available to detect the severity of fetal exposure accurately.[3] It has been reported that the fetus needs five-times longer than the mother's oxygen treatment period.[7,8] Hyperbaric oxygen treatment (HBOT) provides a higher partial pressure of oxygen in the blood, accelerates the CO release from haemoglobin and reduces neutrophil adhesion to the endothelium, so should be of greater benefit than NBOT.[9] However, gross congenital malformations, retrolental fibroplasia, retinal detachment, microphthalmia,

stillbirth, neonatal death, and premature birth were reported in animals exposed to maternal hyperoxia in the 1960s, leading to safety concerns.[10,11] However, there are no studies reporting any adverse effects on human fetuses exposed to HBOT, to the author's knowledge.[7,8] Acute CO poisoning in a pregnant woman is an accepted indication for HBOT according to the Undersea and Hyperbaric Medicine Society (UHMS).[8,9] Nevertheless in several countries, HBOT is still not recommended for pregnant patients except for life-threatening conditions. Evidence on fetal adverse effects of HBOT is lacking.[12] This subject is difficult to investigate, as it is not ethical to conduct randomised controlled prospective human studies to research fetal adverse events. However, clinicians still have two major unanswered questions in this field: the physiological (or pathophysiological) effects on the fetus during HBOT and whether HBOT is effective in preventing CO-related complications in fetuses.

The limited number of HBOT centres and lack of diagnostic methods for use in fetuses have resulted in a paucity of research on fetal outcomes after CO poisoning, with the existing literature being composed mainly of case reports. Long-term follow-up of surviving infants may shed light on the benefits and complications of HBOT; there are only two long-term follow-up studies published in English to date.[8,13]

The present study analysed the long-term outcomes for fetuses treated with HBOT after acute in-utero CO poisoning. Outcomes were classified into three main periods: pregnancy, birth, and after birth. In the first instance, the aim was to determine the undesired fetal outcomes that were associated with CO poisoning or were found to be coincidental. Secondly, the aim was to determine the undesired fetal outcomes associated with HBOT. Finally, an anlysis was undertaken on the effects of clinical severity parameters and pregnancy trimester during the poisoning on long-term fetal outcomes.

Methods

The study was approved by the Ethical Committee of our institution (Approval number 2020/85, date 25/02/2020).

This was a retrospective review of the records of pregnant patients who received HBOT for acute CO poisoning between 01 January 2013, and 01 June 2016. HBOT was carried out in either a monoplace or multiplace chamber at the same single institution which is a regional referral centre for HBOT. Patients may be transported to the centre from other hospitals and from other surrounding cities. The monoplace chamber protocol involved breathing 100% oxygen at 202.6 kPa for 75 minutes (10 minutes compression, 10 minutes decompression) or breathing 100% oxygen via a mask at 243.1 kPa for 90 minutes with a 5-minute air break (15 minutes compression, 15 minutes decompression). The multiplace chamber protocol involved breathing 100% oxygen at 243.1 kPa for three 30-minute periods with 5-minute air breaks (15 minutes compression, 15 minutes decompression). Additional sessions were given daily until maternal symptoms were fully resolved, as assessed by a hyperbaric medicine specialist.

Table 1
Severity grading for CO poisoning[13]

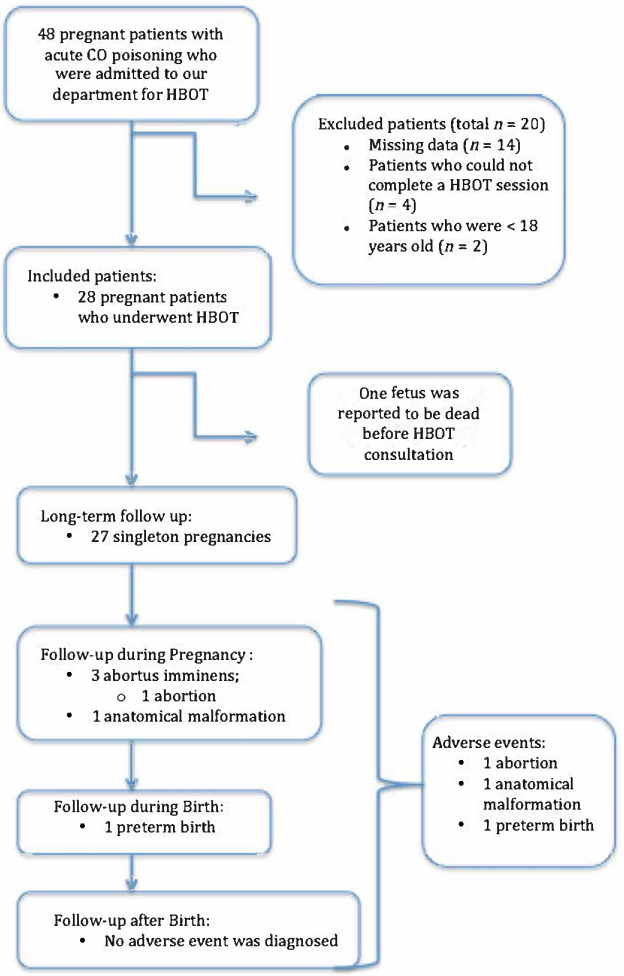
Severity	Symptoms
Grade 0	No symptoms
Grade 1	Alert, oriented
Grade 2	Alert, mental state alterations
Grade 3	Not alert, disorientation
Grade 4	Disorientated, depressed sensorium
Grade 5	Comatose

The carboxyhaemoglobin (COHb), white blood cell (WBC) count, blood pH and lactate level at the time of ED admission, electrocardiogram (ECG), symptoms, week of pregnancy, obstetrician consultation, medical history and the time elapsed before HBOT were reviewed from departmental records. Pregnancy problems after HBOT, birth week, birth weight and height, birth-related problems, age of crawling, walking independently and talking (first words), and the health status of infants were analysed as long-term follow-up parameters from patient records made during telephone interviews with parents. Exclusion criteria were: mother's age < 18 years old; inability to complete one HBOT session; and missing long-term follow-up data.

Clinical severity was classified according a previously published system (Table 1).[13] Additionally, transient/prolonged unconsciousness, cardiac abnormality, COHb level, and HBOT delay were determined as clinical severity parameters. These parameters and pregnancy trimester were compared with long-term infant outcomes (birth week, birth weight, birth height, crawling, walking independently and talking [first words] age). The COHb subgroup cut-off was determined to be 25%, according to the UHMS HBOT indication criteria for acute CO intoxication.[9] The time elapsed before HBOT was divided into two groups, ≤ 6 h and > 6 h delay, for statistical analyses. This cut-off was adopted from studies suggesting that the optimal time for HBOT is as soon as possible, preferably within the first six hours following CO exposure.[14,15]

Data analysis was performed using SPSS Statistics Version 21 (IBM Corp., Armonk NY, USA). The data were reported as *n* (%) and mean (standard deviation). Non-normal data were reported as median (range). The Shapiro-Wilk test was performed to determine the normal distribution of continuous variables. Pearson or Spearman correlation analysis was performed to analyse the linear correlation between variables. The relationship between pregnancy trimester and long-term outcome parameters was analysed with the Kruskal-Wallis test. Further binary comparisons were completed using the Mann-Whitney U test. Chi-square or Fisher's exact test were used for analysis of the

Figure 1
Flow chart of follow-up period and patient selection regimen



comparisons between pregnancy trimester and discrete variables of long-term outcome. The relationship between clinical severity groups, COHb groups, HBOT delay groups, transient/prolonged unconsciousness groups, cardiac abnormality groups, and long-term outcome parameters was analysed by Mann-Whitney U for continuous variables and by Chi-Square or Fisher's exact test for discrete variables. $P < 0.05$ was considered statistically significant.

Results

Forty-eight pregnant patients with acute CO poisoning were admitted to our department for HBOT. Patient selection and follow-up processes are reported in Figure 1. Twenty-eight pregnant patients were included in the present study. The demographic data of the patients during CO poisoning are shown in Table 2. Only one fetus whose mother had presented with Grade 5 severity was reported dead before HBOT consultation. All the remaining patients (n = 27, 96.4%) had reported a normal obstetric examination before HBOT. However, the obstetric consultation report included only whether the fetal heart beat was present or not. Patients' clinical severity and pregnancy trimesters are presented in

Table 2
Demographic and biochemical data of the 27 analysed patients following the CO poisoning incident; CO – carbon monoxide; COHb – carboxyhaemoglobin; HBOT – hyperbaric oxygen treatment; WBC – white blood cells. Note: percentages are calculated on a small sample size

Parameter	Mean (SD) or median [range] or *n* (%)
Age (years)	26.8 (4.9)
Pregnancy week	18 (8.5)
COHb (%)	27.9 [15.6–55.2]
WBC (10^3 cells·uL^{-1})	12,318 (6,602)
pH	7.40 (0.05)
Lactate (mmol·L^{-1})	2.92 (3.03)
HBOT delay (hours)	4 [2–13]
CO source	
Stove	12 (42.9%)
Natural gas	9 (32.1%)
Water heater	6 (21.4%)
Other	1 (3.6%)
Clinical severity grade[13]	
Grade 0	3 (10.7%)
Grade 1	13 (46.4%)
Grade 2	8 (28.6%)
Grade 3	3 (10.7%)
Grade 4	0 (0%)
Grade 5	1 (3.6%)

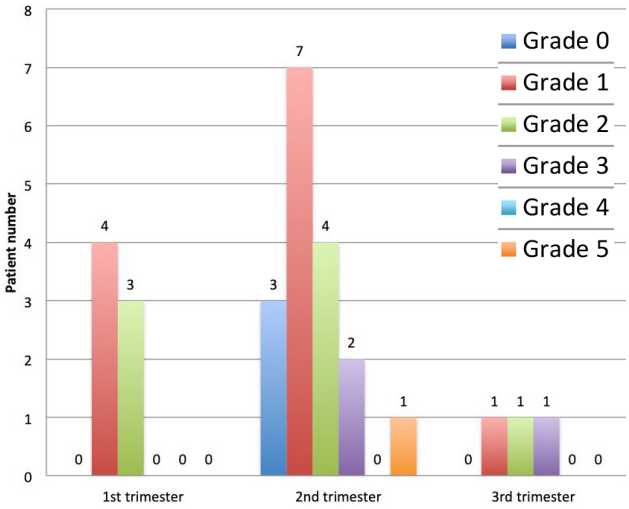
Figure 2. Only one patient's pregnancy trimester information was missing. The median completed HBOT treatment number was 1 (1-2). Twenty-five patients underwent one HBOT treatment, and three patients underwent two HBOT treatments.

The long-term follow-up data were analysed in 27 surviving patients due to one fetus's death before HBOT (Figure 1). Three cases (11.1%) had an abnormal outcome including: abortion (n = 1), premature birth (n = 1), and anatomical malformation (n = 1). Twenty-four of the 27 patients (88.9%) delivered full-term healthy infants with normal birth weight. Six patients (21.4%) continued to smoke during their entire pregnancy. None of the patients reported drinking alcohol during pregnancy.

FOLLOW-UP DURING PREGNANCY AFTER HBOT

Four patients (14.3%) had an abnormal obstetric follow-up, with three patients reported having *abortus imminens*. Only one of these resulted in medical abortion, due to preterm premature rupture of membranes two weeks after the poisoning. This patient (31-years-old, G3P1) had CO poisoning at 16 weeks of gestation with Grade 1 severity. She reported having vaginal bleeding problems for two weeks prior to the HBOT, which also continued afterwards. The

Figure 2
Number of patients by clinical severity (Table 1) and trimester



remaining two patients delivered healthy infants with normal birth weights at 39 weeks of gestation via spontaneous vaginal birth.

One patient (19-years-old, G2P1) who was poisoned at the 11th week of pregnancy had Grade 2 clinical severity. The obstetrician consultation was reported as normal before HBOT, and her headache was fully resolved after one HBOT session. However, a lower extremity malformation of the fetus was diagnosed at the sixth month of pregnancy with ultrasonography. The patient had a spontaneous vaginal delivery at full-term without any complication. At the follow-up interview, the parents stated that the baby had undergone an operation due to spina bifida, and he had undescended testicles (cryptorchidism). The baby was two-years-old but could not crawl yet at the time of the final interview.

BIRTH-RELATED OUTCOMES

Only one preterm birth was reported due to preterm labor. This infant was delivered at the 32nd week of gestation (classified as moderate to late preterm birth according to the World Health Organisation) by Caesarean section and had low birth weight (1.5 kg). The infant was hospitalised in the intensive care unit (ICU) due to prematurity related problems. The mother (28-years-old, G3P2) had previously had another preterm birth by Caesarean section and a history of hypertension. The patient was admitted to the ED with Grade 2 severity CO poisoning at 27 weeks of gestation, and completed two HBOT sessions. At the follow-up interview, the baby was three years old. Her parents stated that the baby was healthy with no medical complaints.

The remaining 26 patients delivered term healthy infants with normal birth weights. The median gestational age at birth was 39 (32–42), and the median birth weight was 3,490 g (1,500–4,080 g). The mean birth height was 48.8 cm (SD 3.61). The detailed birth-related outcomes are available in Table 3.

FOLLOW-UP AFTER BIRTH

After birth, the follow-up was continued for 26 of the infants (due to fetal death/medical abortion). The median age of babies was 34 (8–44) months at the last interview. The mean crawling age was found to be 9.2 (SD 2.1) months. The median age at which the infants walked independently was 12 (10–18) months. The median talking age (first words) was found to be 12 (8–24) months. Only one child, who was 43 months old, could not speak as yet. His parents did not report any diagnosed disease.

RELATIONSHIP BETWEEN CLINICAL PARAMETERS, PREGNANCY TRIMESTER AND LONG-TERM FOLLOW-UP OUTCOMES

Transient/prolonged unconsciousness, cardiac abnormality, COHb groups, HBOT delay groups, and pregnancy trimester were compared with long-term infant outcome parameters (birth week, birth weight, birth height, crawling, walking independently and talking [first words] ages). Only one statistically significant relationship was found, between birth weight and pregnancy trimester during CO exposure (P = 0.029). Further binary comparisons for pregnancy trimester were completed. CO poisonings during the third trimester significantly decreased the birth weight. (1st–3rd trimester P = 0.018, 2nd–3rd trimester P = 0.018) though third trimester numbers were small (n = 3) and this is a fragile result (Figure 3).

The linear correlation between clinical severity parameters (COHb, lactate, WBC, pH, delay of HBOT), pregnancy week, and long-term infant outcome parameters (birth week, birth weight, birth height, crawling age, walking independently age and talking [first words] age) were investigated. There was a modest positive correlation between the week of pregnancy during the incident and the age of walking independently (P = 0.043, r = 0.436). (Figure 4)

Discussion

A single episode of hypoxia from CO poisoning can be teratogenic for a fetus.[3] Thus, acute CO poisoning in pregnancy is accepted as an indication for HBOT.[8,9] The largest three studies reported in the literature document good outcomes in terms of long-term follow-up of infants who were subject to HBOT in utero to treat acute CO poisoning.[8,13,16] A number of case reports also detail uneventful long-term infant outcomes following HBOT.[17,18] However in two reports, persistently small head circumference and bladder complications were demonstrated. Both cases had a severe clinical presentation with maternal COHb > 45%.[19,20] In the present study, one pregnancy ended with miscarriage two

Table 3
Birth related outcomes of 27 pregnancies treated with HBOT after CO poisoning; CS – Caesarean section; LBW – low birth weight; VD – vaginal delivery. Note: percentages are calculated on a small sample size

Parameter	*n* (%)
Birth type	
VD	18 (66.6)
CS	8 (29.6)
Abortion	1 (3.7)
Birth week	
Term	25 (96.2)
Moderate to late preterm (32–37 week)	1 (3.8)
Birth weight	
Normal (> 2.5 kg)	22 (95.7)
LBW (1.5–2.5 kg)	1 (4.3)
Not available	3
Sex	
Female	16 (61.5)
Male	10 (38.5)
Intensive care unit necessity	
Yes	1 (3.8)
No	25 (96.2)

weeks after HBOT sessions, one with preterm birth, and one fetal anatomic malformation was recorded. However, these outcomes are possibly incidental, and not related to CO poisoning or HBOT.

In the case of miscarriage, the patient had a previous miscarriage history: a previous pregnancy loss may increase the miscarriage risk for a consecutive pregnancy.[21] In addition, the patient had been experiencing vaginal bleeds both prior to and after the HBOT, and bleeding is one of the most common signs of miscarriage.[22] In a review about air pollution exposure during pregnancy, the relationship between CO exposure and spontaneous abortion in the first trimester was analysed. However, only three studies were available, and the authors felt that the results were inconclusive.[23] Similarly, another study failed to find evidence to relate abortion and HBOT.[8] Taking all of this into account, the bleeding problems in this pregnancy and miscarriage history demonstrates an apparent risk; therefore, the spontaneous abortion is not likely to be related to CO poisoning or HBOT.

In the second adverse outcome, the pregnancy ended with a preterm birth five weeks after the CO incident. Preterm births after CO poisoning are reported in the literature;[7,13,24] nevertheless, preterm birth in CO intoxicated pregnant cases treated with HBOT are rarely reported. One study reported no adverse events after HBOT, although they did note a preterm birth after NBOT.[13] However, another reported premature delivery of a healthy baby at 35 weeks of gestation in a woman who received HBOT due to acute CO intoxication.[8] In the present study, the mother had a previous preterm birth and a history of hypertension; these factors, along with maternal stress are well-known risk factors for premature birth,[25] and thus are more likely to be causative in this case than CO poisoning or HBOT.

In the case of the baby born with anatomical malformation, the mother had CO poisoning at 11 weeks of gestation; at this point, ultrasound examination was normal. However, a lower extremity malformation was diagnosed in the sixth month of the pregnancy; post-partum, the baby was diagnosed with spina bifida and cryptorchidism. Open neural tube defects are common congenital anomalies, with myelomeningocele (spina bifida) being the most common presentation. Neural tube closure in an embryo occurs during the third and fourth weeks after conception. Failure can result in vertebrae, spinal cord, cranial or brain defects.[26] The neurologic deficit depends on the level of the lesion. Meningomyelocele usually leads to complete paralysis and sensation deficits, affecting lower extremities and trunks.[27] These cases often have congenital skeletal deformities and orthopaedic abnormalities. Folate deficiency, genetic factors, syndromes, amniotic bands, maternal hyperthermia, pre-gestational diabetes, obesity, pesticide exposure, nitrosatable drugs, and clomiphene are risk factors for open neural tube defects.[26] Ultrasound examination and maternal serum alpha-fetoprotein are widely used for detection. Transvaginal ultrasound examinations at 12–14 weeks of gestation have low detection rates for spina bifida (44%), while those made in the second trimester have a 92–95% detection rate.[26] In the present case, the ultrasound was reported to be normal in the 11th week of gestation. Maternal alpha-fetoprotein results were not available. The mother (G2P1), who was 19-years-old, lived in a rural area and the CO poisoning occurred from the burning of dried dung for heating. The mother's young age and lower socioeconomic status are the apparent risk factors for NTD.[28] The infant also had cryptorchidism, which is more common in meningomyelocele than the normal population.[29] In conclusion, the complications in this infant are unlikely to be related to CO poisoning or HBOT based on the fact that the CO poisoning and HBOT occurred in the 11th week after physiological neural tube closure in the embryo would have been completed.

The age of crawling, walking independently, and talking (first words) ages were also studied as infant developmental milestones. In two previous studies, psychomotor development and growth were uneventful in infants who received HBOT in utero.[13,16] Similarly, the crawling and walking milestones were in 'normal age range' according to the World Health Organisation and the normative Turkish values.[30,31] The median age for the use of two words other

Figure 3

Box plot of the relationship between pregnancy trimester during CO poisoning and birth weight of infants; the thick line in the box shows the median. The box represents interquantile range. The bars represent the range of data. Data falling outside the lower (Q1) and upper (Q3) quartile range are plotted as outliers of the data

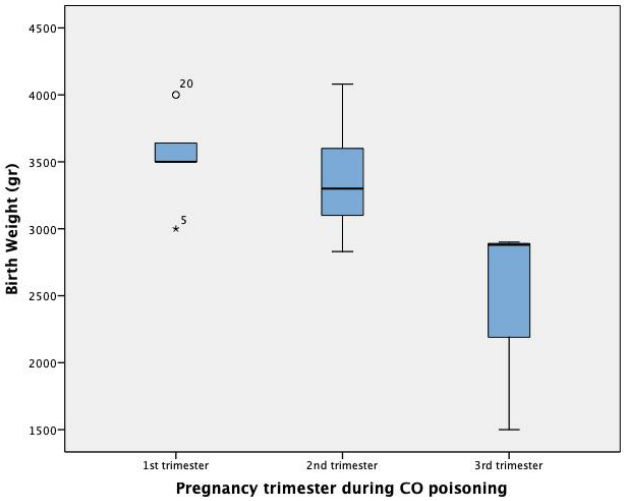
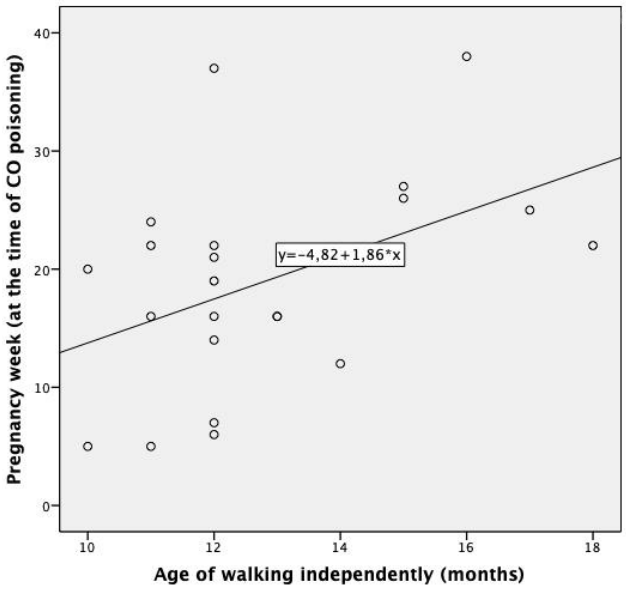


Figure 4

The relationship between pregnancy week during CO poisoning and infants age of walking independently



than mama/dada was reported to be 11 (9.1–14.9) months in a Turkish language development milestones study.[32] Six infants in the present study completed this developmental milestone much later, after 15 months of age. However, these data were gathered retrospectively by telephone interviews with parents in which they might not have remembered correctly or misunderstood the question.

The final aim was to determine the relationship between clinical severity parameters and pregnancy trimester with long-term outcomes of infants who underwent HBOT in utero for acute CO intoxication. Most case reports in the literature are limited with respect to severe CO poisoning pregnant cases.[18–20] Only one compared the severity of the CO exposure and pregnancy trimester at the time of the incident with infants' long-term outcomes. That study found that only severe cases (Grade 4 and 5 severity, $n = 5$) had adverse events in the long-term follow-up. The severe cases without any adverse event during follow-up ($n = 2$) had all received HBOT.[13] None of the present cases following which a live infant was born had Grade 4 or 5 severity; thus, it was not possible to compare these severity groups with long-term outcomes.

Birth weight is a significant indicator of intrauterine growth retardation and is affected by many factors.[33] Low or chronic CO exposure in utero may also affect birth weight.[16] However, the relationship between pregnancy trimester during CO poisoning and birth parameters has received very little attention.[8,16] One study found that the pregnancy trimester in which exposure occurred did not affect mean birth weight.[13] In contrast, CO poisonings during the third trimester were significantly associated with a decrease in birth weight in the present study ($P = 0.018$). To date, trimester effects on birth weight have only been studied with regard to maternal smoking exposure;[34] in a meta-analysis all fetal size, and growth measurements were significantly reduced at the third-trimester. However, maternal smoking did not significantly affect the estimated fetal weight or abdominal circumference in the second trimester.[34] In the present study, only one infant had a low birth weight, only six mothers were active smokers during pregnancy, and every infant had completed at least one HBOT session in utero with 4 (2–13) hours median HBOT delay after CO exposure. However, with such small sample sizes it is impossible to draw a reliable conclusions from these data. The effect of pregnancy trimester on birth weight for CO intoxications should be studied in further clinical trials with greater sample sizes.

The week of pregnancy during poisoning was found to have a modest positive correlation with the age of independent walking ($P = 0.043$, $r = 0.436$), which suggests that the older the fetus at the time of CO poisoning, the more delayed the walking age. Genetic and environmental factors influence walking attainment.[35] However, no other studies have revealed a relationship between CO intoxication and the infant's walking age. On the other hand, delay in walking may be a predictor of a developmental disorder such as cerebral palsy.[35] Cerebral palsy is a known complication of CO poisoning during pregnancy, especially in the last trimester due to hypoxia; however none of the infants in the present study were diagnosed with cerebral palsy.[6] All of the infants in the present cohort could walk before the 18th month, except the infant with lower extremity malformation. Thus, the observation is insufficient to draw a reliable conclusion, and further studies may focus on the mothers' gestational age and infants' developmental outcomes.

The present study covers the largest pregnant patient group receiving HBOT for CO poisoning with the longest follow-up period (8–44 months) in the literature and includes pregnancy, birth, and neurological/motor developmental outcomes. Only one other study is similar in terms of the study population; however follow-up ended at birth.[8] Another similar study did not investigate the effect of HBOT on infants' developmental milestones,[13] while a third compared the effect of HBOT on infants with a normal, non-treated population in terms of only psychomotor development and growth. They did not analyse adverse events during pregnancy and birth.[16]

LIMITATIONS

Important limitations were the absence of an NBOT -treated control group and the absence of Grade 4–5 clinical severity cases. The retrospective nature of the study also lead to the loss of some valuable data; for instance, fetal monitoring tracings of late decelerations, fetal movements, biophysical profile score and head circumference were not recorded. Another concern is that the long-term outcomes were gathered from interviews with parents, who may not have remembered developmental milestones correctly or misunderstood questions. Neurological and motor developmental milestones were limited to crawling, walking independently, and talking (first words). HBOT was mostly completed in only one session in our study. Mothers were unwilling to continue additional HBOT sessions if their symptoms resolved after one session. However, as fetal status cannot be measured effectively, there is no consensus on the optimal total HBOT session number and this could not be analysed in this study.

Conclusions

The adverse events seen in this cohort were likely to be incidental. There was no definite evidence of fetal morbidity or mortality after HBOT for CO poisoning. HBOT may improve short-term and long-term outcomes without any complication in infants poisoned with CO in utero, though definitive conclusions cannot be drawn from a retrospective observational cohort study. Prospective controlled studies with a larger sample size would bring more certainty to conclusions, but may be challenging ethically. Objective data on fetal distress after CO poisoning and HBOT should be gathered prospectively. Similarly, significant developmental indicators such as head circumference at birth should also be included in these studies. Further studies may also focus on describing the best HBOT protocol (total number of sessions) and the optimal time window for the first HBOT session. The relationship between clinical severity parameters and infant outcomes should also be studied to determine the most vulnerable group. In this way, the treatment protocols may be extended for better infant outcomes in high-risk groups.

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Effect of hyperbaric oxygen treatment on patients with reduced left ventricular ejection fraction

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Abstract
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Introduction: Hyperbaric oxygen treatment (HBOT) is available to a wide spectrum of patients, many with significant co-morbidities. Considering its effects on cardiac physiology and reports of pulmonary oedema following exposure, concerns exist about the safety of patients with compromised cardiac function. Few studies have described adverse events occurring during HBOT and even fewer reports address events arising in the hours following HBOT. A relation between adverse events and cardiac function has not been established. As medical guidance is limited, we aimed to evaluate the risk for patients with reduced left ventricular ejection fraction (LVEF) receiving HBOT.

Methods: This retrospective chart review of patients receiving HBOT from April 2003 through December 2019 at our hospital was designed to describe clinical characteristics of patients and to identify adverse events during HBOT and within 24 hours after HBOT. Patients ≥ 40 years of age with a documented LVEF of ≤ 40% were included. Data are presented as mean (SD) [range] or counts, as appropriate.

Results: A total of 23 patients were included in the final analysis, 2 (1) [0–4] patients per year. Patients received 25 (19) [1–60] treatments. Two patients had an episode of acute decompensated heart failure possibly linked to HBOT.

Conclusions: This study described the clinical characteristics of patients with reduced LVEF receiving HBOT and showed reassuring results, with a majority of patients with reduced LVEF tolerating HBOT well. Prospective research is required to more fully assess the risk.

Introduction

Hyperbaric oxygen treatment (HBOT) is an adjunctive modality that has shown benefits for a wide variety of pathologies. The Undersea and Hyperbaric Medical Society (UHMS) has identified 14 approved indications.[1] The European Committee on Hyperbaric Medicine (ECHM) agrees with a majority of the UHMS indications (except for severe anaemia), and provides a broader list of indications.[2] HBOT is an option for a large spectrum of patients, some with significant co-morbidities, including a high prevalence of cardiovascular problems.

HBOT uses 100% oxygen delivered at a pressure of 202.6–303.9 kPa (2–3 atmospheres absolute [atm abs]). Hyperoxia acts in numerous ways, many affecting haemodynamics and cardiac physiology. It is potentially responsible for an increased oxidation of nitric oxide (NO) radicals, which results in arteriolar vasoconstriction that increases systemic vascular resistance. Hyperoxia also stimulates vagal activity, causing bradycardia. An uneven effect on right and left ventricular contractility, a decrease in left ventricular compliance, and an increased oxidative myocardial stress[3] that possibly persists up to one hour after HBO exposure[4] have also been described. A measure of this myocardial stress has been evaluated indirectly with N-terminal pro-B-type natriuretic peptide (NT-proBNP) in diabetic patients without cardiovascular disease, before and after exposure to HBOT. An increase in NT-proBNP was interpreted to mean that a considerable ventricular wall stress may be induced by HBOT.[5] However, these findings must be considered preliminary since brain natriuretic peptide (BNP) and NT-proBNP levels tend to be higher in persons with diabetes, making it difficult to extrapolate these observations to a non-diabetic population.

Bradycardia, decreased ventricular compliance and myocardial stress are all responsible for a decreased cardiac

output that has to overcome an increased afterload caused by a rise in systemic resistance. These effects could put patients in a hyperbaric chamber at risk of relative volume overload during HBOT. When hyperoxia ceases at the end of treatment, a reversal in the haemodynamic changes develops; peripheral resistances drop and the vagal stimulation causing bradycardia ceases. The fall in peripheral resistance and the increase in heart rate will increase cardiac output in order to maintain an adequate blood pressure, causing another strain on the heart and another risk of relative volume overload after exposure.

When these changes are applied to an already compromised left ventricle, they can potentially exceed the capacity of the ventricle to further manage pressure, putting a patient with reduced left ventricular ejection fraction (LVEF) at higher risk of pulmonary oedema. This rare but potentially life-threatening complication has been reported in HBOT with an estimated incidence of 0.1%.[3] There are at least four case reports of pulmonary oedema associated with HBOT in patients with cardiac disease with reduced LVEF or significant valvulopathy.[6,7] The moment when the first symptoms appear may be important. Except for one case, symptoms all occurred during HBOT. One case described symptoms that developed immediately after decompression, as the patient was exiting the chamber. The timing in these cases could indicate a risk for pulmonary oedema during or immediately after the conclusion of the treatment.

These observations raise important concerns about the safety of patients with compromised cardiac function receiving HBOT. Medical guidance for at-risk patients with reduced LVEF is limited. The objective of this study was to gain a better understanding of the risk, in term of cardiovascular impact, of HBOT for patients with reduced LVEF.

The specific aims of this study were to:
1) Describe the pre-HBOT clinical characteristics of patients with reduced LVEF being treated in the hyperbaric chamber of our facility; and
2) Identify cardiovascular adverse events, including acute decompensated heart failure, during HBOT and within 24 hours after HBOT that could have been triggered by HBOT or the cessation of HBOT.

Methods

The Comité d'éthique de la recherche (CER) du CISSS de Chaudière-Appalaches approved the retrospective study. A waiver of consent was provided for the review of charts of patients receiving HBOT in the hyperbaric chamber of Hôtel-Dieu de Lévis in Chaudière-Appalaches, Québec, between April 2003 and December 2019. The treatments were received in a monoplace chamber from April 2003 to June 2012, then in a multiplace chamber. Oxygen was delivered via a hood for every patient.

Inclusion criteria were: age ≥ 40 years at the time of the treatments and a documented reduced LVEF, with an imaging modality (echocardiogram, nuclear stress test, or cardiac MRI) reporting a LVEF of ≤ 40%; or with a LVEF of ≤ 40% written in the patient's medical history if no imaging report was available. Patients were treated as new cases if there was more than 12 months between treatment cycles, considering that their basic characteristics, indication for HBOT, and LVEF could have changed over time. Patients under the age of 40 years of age were excluded due to the low prevalence of heart failure in the younger population.

Patient selection was performed by an internal medicine resident, using the hyperbaric chamber database and the Hôtel-Dieu de Lévis' electronic charts. Charts from other facilities were not accessible. The hyperbaric chamber database was first used to screen patients.

When a patient met the age inclusion criterion, a list of his or her medical conditions was evaluated. The medical summary of the hyperbaric chamber database was first used when available. The hospital's charts were then screened for more details on cardiac function based on imaging and consultations, mainly in cardiology and internal medicine. Every LVEF report in the patient's chart was recorded. The closest report available either before, during, or after HBOT was considered as the patient's LVEF during the treatments, with a maximum time period of 60 months before the first treatment and two months after the last treatment. If LVEF results were available from two different imaging modalities within one month, the lowest valid value was registered as the patient's LVEF. If there was a difference of more than five percent between the two imaging modalities, the cases were reviewed by the research team. A conservative position was taken to exclude cases that could have been falsely low. Thus, if the closest report to HBOT stated a LVEF > 40%, the patient was excluded from the study.

The hospital's charts were used to find basic clinical characteristics (age, sex, region of origin, co-morbidities, aetiology of heart failure) and any reported adverse events. Every treatment received by a patient was recorded as a single entry and adverse events were associated with specific treatments.

Adverse events were first classified according to their temporal proximity to HBOT. Adverse events 'during HBOT' occurred when the patient was in the hyperbaric chamber, from the beginning of the treatment through to exiting. Adverse events of particular interest were signs and symptoms of a cardiovascular complication, such as acute pulmonary oedema, progressive dyspnoea, chest pain, symptoms of peripheral oedema or neurologic symptoms such as confusion. The hospital's chart provided access to a treatment sheet filled by a hyperbaric centre nurse following each treatment, with descriptions of vital signs (heart rate, blood pressure, oxygen saturation) and any symptoms.

Adverse events 'within 24 hours after HBOT' occurred from the moment the patient was out of the hyperbaric chamber up to 24 hours later, or until re-entering the chamber if the next treatment began within 24 hours.

Adverse events were described with all available details. These included charted signs and symptoms, patient reports, and medical reports with description of symptoms and final diagnosis of any visit to the emergency room. Objective elements that suggested an investigation done for a possible cardiovascular event were noted. Imaging modalities (chest X-ray, electrocardiogram, telemetry reports, and echocardiograms) and laboratory values (troponins and BNP) were assessed.

Once data collection was complete, the research team reviewed every adverse event to evaluate the cardiovascular relevance. Adverse events were classified as '*inconsequential from a cardiovascular perspective*', '*probably not linked to HBOT*', and '*possibly linked to HBOT*'. Adverse events considered inconsequential were symptoms and complications not specific to a cardiovascular event, including common symptoms associated with HBOT or symptoms that the medical team did not consider as needing further investigation. They included otalgia, anxiety, diaphoresis, discomfort, and complications such as hypoglycaemia and convulsions. Adverse events of principal interest were signs, symptoms, and objective elements suggesting an acute cardiovascular event (dyspnoea, chest pain, peripheral oedema, electrocardiogram (ECG) changes, chest X-ray, troponins, BNP, emergency room and cardiology consults and hospitalisations). These adverse events were discussed within the research team to classify them as probably not linked to HBOT or possibly linked to HBOT. They were classified as probably not linked to HBOT when an alternative diagnosis was more probable or when the results of subsequent investigations were normal. Adverse events that could not be satisfactorily explained by another condition or with abnormal test results were classified as possibly linked to HBOT. Cardiovascular adverse events possibly linked to HBOT were further discussed to assess their specificity regarding acute decompensated heart failure.

Data are presented as mean (SD) [range] or counts and percentages, as appropriate. Fisher's exact tests were used to compare adverse event rates in the first five serial HBOT treatments (considered to reflect inexperienced patients) versus the sixth and more serial HBOT treatments (considered to reflect experienced patients), to determine if experience with the hyperbaric environment and procedures played a role in adverse incident rates. Significance was accepted at $P < 0.05$.

Figure 1
Patient selection paradigm

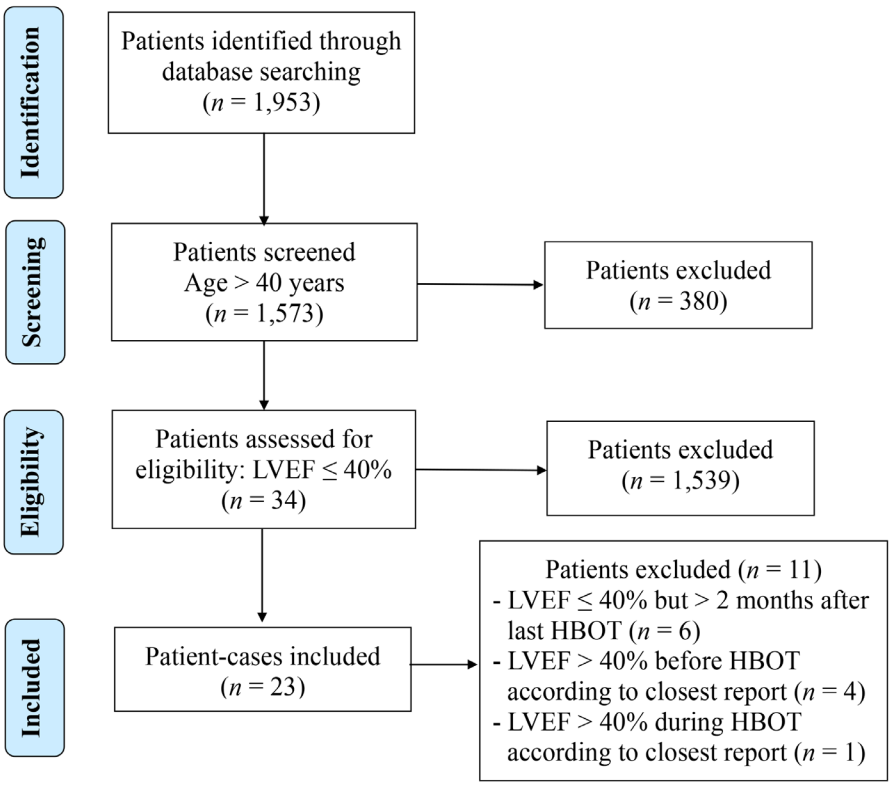

Table 1

Patient and HBOT characteristics; COPD – chronic obstructive pulmonary disease; HBOT – hyperbaric oxygen treatment. Note: percentages are calculated on small sample sizes

Parameter	All	Male	Female
Cases, *n* (%)	23	20 (87)	3 (13)
Age in years, mean (SD) [range]	69 (8) [51–83]	70 (8) [51–83]	63 (5) [58–68]
Treatments, total	564	477	87
Treatments, mean (SD) [range]	25 (19) [1–60]	24 (19) [1–60]	29 (26) [1–53]
Indication for HBOT, *n* (%)			
Improve wound healing	13 (57)	10 (50)	3 (100)
Osteoradionecrosis	6 (26)	6 (30)	0 (0)
CO intoxication	2 (9)	2 (10)	0 (0)
Osteomyelitis	1 (4)	1 (5)	0 (0)
HBOT challenge	1 (4)	1 (5)	0 (0)
Aetiology of heart failure, *n* (%)			
Ischaemic	21 (91)	18 (90)	3 (100)
Ischaemic vs. Takotsubo	1 (4)	1 (5)	0 (0)
Ischaemic + hypertensive	1 (4)	1 (5)	0 (0)
Comorbidities, *n* (%)			
Cardiovascular disease	23 (100)	20 (100)	3 (100)
Peripheral artery disease	17 (74)	15 (75)	2 (67)
Hypertension	14 (61)	11 (55)	3 (100)
Dyslipidaemia	14 (61)	11 (55)	3 (100)
Diabetes mellitus	13 (57)	10 (50)	3 (100)
History of cancer	9 (39)	8 (40)	1 (33)
Pacemaker	8 (35)	7 (35)	1 (33)
Chronic kidney disease	6 (26)	4 (20)	2 (67)
Atrial fibrillation	5 (22)	4 (20)	1 (33)
Obesity	4 (17)	2 (10)	2 (67)
COPD	3 (13)	3 (15)	0 (0)
Hypothyroidism	3 (13)	2 (10)	1 (33)
Anaemia	3 (13)	2 (10)	1 (33)
Cirrhosis	1 (4)	1 (5)	0 (0)
Sleep apnoea	1 (4)	1 (5)	0 (0)
Epilepsy	1 (4)	1 (5)	0 (0)

Results

A total of 1,953 patients received at least one HBOT treatment between April 2003 and December 2019 (Figure 1). Of these, 380 were excluded because they did not meet the age criteria, 1,539 because they did not have a documented reduced LVEF ≤ 40%, and 11 because they had no reports within the inclusion range for HBOT timing. Two patients were entered as separate cases for two different treatment cycles, with time between cycles of 43 and 71 months. The final study group consisted of 23 patients (20 male, three female; 69 (8, [51–83]) years of age), for an accrual rate of 2 (1, [0–4]) per year.

The clinical characteristics of the study group are presented in Table 1. Patients received 25 (19, [1–60]) treatments, with the most frequent indications for HBOT being to improve wound healing (*n* = 13, 57%). Every patient had ischaemia as the aetiology of heart failure. One patient had an alternative diagnosis of Takotsubo, a usually transient stress cardiomyopathy. The most frequent co-morbidities were cardiovascular disease (all 23 patients) and peripheral artery disease (74%). Direct access to charts was available for 57% of the patients.

Two patients had imaging modalities done within a month of each other with marginal LVEF differences (28% vs. 30–35% and 30% vs. 35%). Two patients had greater

Table 2
Reporting and quantification of left ventricular ejection fraction; HBOT – hyperbaric oxygen treatment. Note: percentages are calculated on small sample sizes

Parameter	All *n* = 23	Male *n* = 20	Female *n* = 3
Available report	16 (70)	14 (70)	2 (67)
Unavailable report	7 (30)	6 (30)	1 (33)
Imaging modality, *n* (%)			
Transthoracic echo	14 (61)	12 (60)	2 (67)
Nuclear stress test	5 (22)	5 (25)	0 (0)
Transoesophageal echo	1 (4)	1 (5)	0 (0)
Unknown	3 (13)	2 (10)	1 (33)
Left ventricular ejection fraction, *n* (%)			
40	4 (17)	3 (15)	1 (33)
35–39	6 (26)	5 (25)	1 (33)
30–34	8 (35)	7 (35)	1 (33)
25–29	3 (13)	3 (15)	0 (0)
20–24	2 (9)	2 (10)	0 (0)
Time from HBOT, *n* (%)			
1–2 month after HBOT	1 (4)	1 (5)	0 (0)
During HBOT	5 (22)	5 (25)	0 (0)
Before HBOT	17 (74)	14 (70)	3 (100)
< 12 months before	12 (52)	10 (71)	2 (67)
13–24 months before	2 (9)	2 (14)	0 (0)
25–60 months before	1 (4)	0 (0)	1 (33)
Unknown	2 (9)	2 (14)	0 (0)

differences in their imaging reports; one remained in the study group with the highest LVEF value kept, and one was excluded because his highest LVEF value was above the cut-off. Imaging reports were available for 16 patients (70%) (Table 2). In three patients (13%), the LVEF value was based on data found in the chart before HBOT but the type of imaging modality and the reports could not be found. The time between the report and HBOT was 9 (8) months for reports available before HBOT (*n* = 15, 65%). The LVEF value was found in a time period of 12 months before HBOT until two months after the last treatment in 18 patients (78%).

Sixteen distinct patients (70%) experienced at least one adverse event of any type in the study period (Table 3), with 3 (6, [0–25]) reported adverse events per patient.

Adverse events considered as cardiovascular in nature but classified as probably not linked to HBOT (*n* = 31, 32%) were found in five patients (22%). These included dyspnoea, confusion, chest pain, and hospitalisation potentially explained by another condition as stated in the chart by the medical team or with normal investigations. For example, one patient had multiple episodes of dyspnoea and mild pulmonary oedema on a chest X-ray with no temporal association with HBOT that was explained by his altered renal function necessitating chronic dialysis.

Adverse events considered as cardiovascular in nature and possibly linked to HBOT (*n* = 17, 18%) were reported in four distinct patients (17%), (60–74 years of age), three of whom reported an adverse event within 24 hours after HBOT, and one who report an adverse event during HBOT and another within 24 hours after HBOT. Two of them received HBOT to improve wound healing, one for osteomyelitis, and one for carbon monoxide (CO) intoxication. They received 1–38 treatments. The reduced LVEF was due to coronary artery disease, with one patient having a possible diagnosis of Takotsubo cardiomyopathy. One patient (male, LVEF 36%) had a diagnosis of non-ST elevation myocardial infarction (NSTEMI) following HBOT. Over a period of three weeks, he presented multiple episodes of chest pain and dyspnoea within 24 hours after HBOT, and one episode during HBOT. Symptoms were reproducible with exercise.

Table 3
Occurrence and classification of adverse events, based on data from 23 patients and 564 patient treatments; *A total of 16 distinct patients had an adverse event of any type. Patients may be entered twice in the table if they reported adverse events in different categories

Parameter	Cardiovascular adverse events				Non-cardiovascular adverse events		Total
	Possibly linked to HBOT		Probably not linked to HBOT				
	During HBOT	≤ 24 h after HBOT	During HBOT	≤ 24 h after HBOT	During HBOT	≤ 24 h after HBOT	
Events (*n*)	1	16	4	27	49	0	97
Patients* *n* (%)	1 (4)	4 (17)	2 (9)	3 (13)	11 (48)	0 (0)	
Treatments *n* (%)	9 (2)		23 (4)		38 (7)		70 (12)
Adverse events per patient overall, mean (SD) [range]							3 (6) [0–25]

Investigations done by the hyperbaric team were always negative. Twelve hours after his 38th treatment, he presented to the ER describing chest pain that began two hours before. Troponins were positive, but no signs of pulmonary oedema were seen on the chest X-ray. He was treated for a NSTEMI, evaluated with coronary angiography, and benefited from revascularisation.

A second patient (male inpatient, LVEF 30%), became confused during his third HBOT treatment and was hypoxaemic and febrile when sent back to his room two hours post-HBOT. He expressed no complaints, and the chart had no mention of decompensated heart failure. Eighteen hours later, a chest X-ray showed mild pulmonary oedema and the oxygen requirements were the same as before HBOT. HBOT was discontinued. His LVEF improved one month later to 66%, making the diagnosis of Takotsubo cardiomyopathy possible.

Finally, two patients were sent to the intensive care unit (ICU) with possible signs of decompensated heart failure. The first (male, LVEF 39%) was treated for CO intoxication and then sent to the ICU immediately after treatment because of neurologic symptoms (somnolence and agitation). Considering the elevated troponins, the cardiology team concluded that myocardial necrosis secondary to CO intoxication was more probable than acute coronary syndrome. The echocardiogram done on the day after HBOT showed reduced LVEF, possibly chronic, since regional wall motion abnormality was mentioned, but no older imaging report was available to confirm this. Chest X-rays before and after HBOT were similar, with no signs of acute decompensated heart failure. A diagnosis of cardiomyopathy secondary to CO intoxication was written in his chart. The second patient (male, LVEF 20–25%) was transferred to the ICU 18 hours after HBOT. His first treatment in the morning was well tolerated and the evening was unremarkable according to the charts. Twelve hours after HBOT, he developed tachypnoea, hyperthermia, hypotension (80/50 mm Hg) with desaturation, and an altered level of consciousness. He was transferred to the ICU and volume repletion started. A cardiology consultation completed on the following day noted pulmonary oedema on the chest X-ray and diffuse ischaemia on the ECG, both done 18 hours after HBOT. Diuretics were administered. The final diagnosis of the ICU team was mixed shock; septic and cardiogenic.

The majority of adverse events ($n = 49$, 51%) were classified as inconsequential from a cardiovascular perspective. They included non-specific symptoms such as otalgia (the most common), headache, discomfort, diaphoresis, nausea, vomiting, and anxiety. They led to premature cessation of a single treatment in one patient and to the cessation of HBOT in two patients.

Fisher's exact testing showed a greater rate of adverse events in patients classified as inexperienced compared to those classified as experienced (26/89 [29%] vs. 44/475 [9%]; $P < 0.0001$).

Discussion

These results show that a majority of patients identified with LVEF between 20 and 40% appeared to tolerate HBOT without serious cardiovascular events.

Higher rates of adverse events were reported in inexperienced patients, mostly inconsequential adverse events from a cardiovascular perspective. Three patients reported adverse events possibly linked to HBOT in the first five serial treatments.

HBOT can impart potentially important stressors on heart physiology during or following exposure. BNP levels are a useful marker of cardiac failure as it increases rapidly in response to myocardial wall stress due to pressure overload, but these values were not documented in any charts. This is not surprising since BNP levels are not routinely assayed in stable patients without signs of acute decompensation in heart failure. It is possible that such assays could be helpful to better understand potential repercussions of HBOT in patients with reduced LVEF.

Patients with compromised cardiac function demonstrate fragility and are at risk of decompensation when confronted with any number of stressors, not limited to anaemia, arrhythmia, infections, ischaemia, intoxications, volume overload, and medication changes. The importance of individual and/or combined stressors cannot be determined in the present work. With the data available, we believe that three of the four distinct patients with cardiovascular events possibly linked to HBOT had other factors that could explain the event, such as significant coronary artery disease, infection or CO intoxication. Three of the four distinct patients with reported adverse events possibly linked to HBOT had signs or symptoms of ischaemia that manifested at distance from the pressurisation. These symptoms were attributed to an acute coronary syndrome, rather than to HBOT. However, we cannot exclude that some of these symptoms can also be attributed to HBOT. It is not surprising that the treatment itself was well tolerated; by delivering 100% oxygen at high pressure, HBOT dramatically increases dissolved blood oxygen content, improving tissue oxygenation. HBOT has been described as beneficial for myocardial infarction following CO intoxication.[8]

Acute decompensated heart failure was not reported during HBOT, nor immediately upon cessation of HBOT. This result contrasts with reports by other authors,[6,7] in which all patients reported symptoms during their treatments or immediately after HBOT. Only one patient in our study had an adverse event possibly linked to HBOT during HBOT. The patient had dyspnoea during one treatment, but the final diagnosis of NSTEMI was made many treatments later, 12 hours after HBOT. One patient was immediately transferred to the ICU after HBOT, but for neurologic symptoms without signs or symptoms of acute decompensated heart failure. All other adverse events reported happened within 24 hours after HBOT, occurring between two and 12 hours, and included no mention of symptoms developing in the minutes when the patients came out of the chamber.

Acute heart failure was reported for two patients within 24 hours following HBOT. Analysis of the data could not isolate HBOT as a causal agent as concomitant factors were present in every reported case of adverse events possibly linked to HBOT. The patient with Takotsubo cardiomyopathy possibly showed signs of decompensation related to HBOT, but missing data prevents us from making this conclusion and we cannot exclude that HBOT could be a precipitating factor.

LIMITATIONS

Our study had several limitations, primarily related to data completeness. Because of the absence of a documented LVEF in many charts, patients with reduced LVEF may have been excluded. Accepting imaging reports that were somewhat removed from HBOT may also have introduced error. The majority of medical records held outside of Hôtel-Dieu de Lévis charts were unavailable for assessment. Patients transferred from another medical centre often had only a brief description of their co-morbidities, without any report of their cardiac function. Even with a majority of patients living in the Chaudière-Appalaches' region, consults done in another hospital or clinic were not available. Any hospitalisation, consult to the emergency room, imaging modality or laboratory value done outside Hôtel-Dieu de Lévis hospital was likely missed. Internal records were also incomplete in some cases. For adverse events occurring during HBOT, signs and symptoms were often found in the chart, but information about more specific characteristics of symptoms, vitals signs and/or diagnosis was often lacking. Some patient files also had imaging reports and/or laboratory values without description of symptoms or reason for these investigations. It is also possible that some adverse events, most likely minor ones that were not considered concerning, were not reported to or documented by the medical team.

Conclusions

HBOT is used to treat many conditions, often in patients with severe co-morbidities. It is not uncommon for the medical team of the hyperbaric chamber to evaluate the eligibility to HBOT of patients who have reduced LVEF.

Concerns have been expressed over a possible risk of precipitating heart failure in patients with reduced LVEF, but medical guidance is not firmly established. We retrospectively evaluated a group of patients with a LVEF ≤ 40% receiving HBOT with reassuring results; the majority of these patients tolerated HBOT well and concomitant stressors and co-morbidities unrelated to the hyperbaric treatment could, at least partially, explain the small number of cases of decompensated heart failure that we considered possibly related to HBOT.

It is possible that HBOT may play a role in increasing the risk of acute decompensated heart failure for patients with a reduced LVEF, but we did not see strong evidence of this. We believe that a low LVEF should not be considered an absolute contra-indication to HBOT, but the risk-benefit relationship must still be considered on an individual patient basis. Prospective studies employing systematic cardiological evaluation would provide additional useful information.

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Regular medication use by active scuba divers with a declared comorbid medical condition and victims of scuba and snorkelling-related fatalities

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Key words
DAN – Divers Alert Network; Diving deaths; Diving incidents; Health status; Pharmacology; Recreational diving

Abstract
(Taylor SE, Taylor DM, Pisasale D, Booth K, Lippmann J. Regular medication use by active scuba divers with a declared comorbid medical condition and victims of scuba and snorkelling-related fatalities. Diving and Hyperbaric Medicine. 2021 September 30;51(3):264–270. doi: 10.28920/dhm51.3.264-270. PMID: 34547777.)
Introduction: The aim of this study was to describe the nature of regular medications taken by active comorbid scuba divers (having a declared medical comorbidity) and scuba divers and snorkellers who died following a diving incident.
Methods: We undertook a retrospective, observational study from July to October, 2020. Data on 268 active comorbid divers were obtained through a 2013 survey of Divers Alert Network Asia-Pacific members. Data on 126 deceased scuba divers and 175 deceased snorkellers were obtained predominantly from 2001–2013 reports to Australian State Coronial Services.
Results: The active comorbid divers were significantly older, less likely to be male, and more likely to be taking one or more medications than the two deceased subject groups ($P < 0.001$). Cardiovascular, endocrine and psychotropic medications accounted for 53.4%, 9.9% and 6.4% of all medications taken, respectively. Almost one tenth of the deceased divers took at least one psychotropic medication, a proportion significantly greater than the other groups ($P = 0.01$).
Conclusions: Medication use among active comorbid divers is common which likely reflects their declared medical condition. Nevertheless, they appear to be diving relatively safely, often with conditions once thought to be absolute contradictions to scuba diving. The deceased divers took significantly more psychotropic medications. It is possible that their underlying psychological/psychiatric conditions rendered them more at risk of a diving incident. Increased vigilance for psychological conditions may need to be considered during diving medical examinations.

Introduction

The scuba diving population is aging.[1,2] Concurrent with this is the increasing prevalence of medical comorbidities among divers, some of which may have significant implications for diving safety, specifically cardiovascular and respiratory diseases, and diabetes.[3–5] In fitness to dive evaluations, the simple presence or absence of a comorbidity is a blunt discriminator of its importance. For example, there is likely a considerable difference between diabetes being managed only by diet and exercise compared to being managed with a strict regimen of frequent insulin injections. Given this, scrutiny of a potential diver's medication regimen is of importance.

Traditionally, the main concerns about medications taken by scuba divers have involved medications to reduce the risk of ear barotrauma[6,7] and motion sickness.[8,9] More recently, increasing numbers of aging divers and snorkellers have reported taking a broad range of regular medications, mainly for cardiovascular conditions.[5,10–13] Concerns about the interactions of some medications with the hyperbaric environment have been described.[9,13–16] Some medications (e.g., angiotensin-converting-enzyme inhibitors [ACE-I]) affect fluid balance and vascular tone and may compound the cardiac effects of immersion. Others (e.g., beta-blockers) reduce exercise tolerance and may limit a diver's ability to deal with exertional requirements. Some may cause drowsiness (e.g., benzodiazepines), increase the likelihood of narcosis (e.g., antihistamines) or lower the seizure threshold (e.g., tramadol).[16]

Given these theoretical concerns, the use of regular medications among victims of scuba diving fatalities has raised questions about the contribution that their medications may have had. Sometimes it is difficult to determine if it is the medications themselves or the underlying comorbidities that may have contributed to the death. Although respondents to a recent survey[10] reported no significant problems associated with their medication use, this was a relatively small survivor

cohort and further research involving larger groups of divers is required to better understand this area of potential risk. In exploring this issue, a 2019 systematic review concluded that there is no evidence of significant risk due to changes in medication mechanisms in the hyperbaric environment and that most medications are not contraindications to diving.[14] However, it was acknowledged that the available evidence is limited and called for additional human studies.

This study aimed to comprehensively describe the nature of regular medications taken by three subject groups: active comorbid scuba divers, and victims of scuba diving or snorkelling-related fatalities. It is hypothesised that, if comorbidities were a significant contributor to diving and snorkelling fatalities, the pattern of medication use across the three groups would be similar.

Methods

We undertook a retrospective, observational study using existing data sources. Data on active comorbid scuba divers were obtained through a 2013 anonymous, online, cross-sectional survey of adult Divers Alert Network Asia-Pacific (DAN AP) members with a declared medical condition. The survey methodology is described in detail elsewhere.[10] Data on victims of scuba diving and snorkelling-related fatalities (deceased divers and deceased snorkellers, respectively) were obtained from reports to various Australian State and Territory Coronial Services on fatalities that occurred during 2001–2013, inclusive. This involved a comprehensive key word search of the National Coronial Information System (NCIS).[17] The methodology for identifying relevant NCIS cases is described in detail elsewhere.[11,18] For snorkelling-related fatality cases prior to 2004, data were obtained from coronial reports in conjunction with relevant Project Stickybeak reports.[19–21]

Ethics approval for the components of data collection were variously obtained from the Human Research Ethics Committees of Austin Health, Royal Prince Alfred Hospital, Deakin University, the Victorian Department of Justice, the Coroner's Court of Western Australia, and the Queensland Office of the State Coroner.

Data on demographics (age, gender) and regular medication use were extracted electronically from the data sources. Two hospital pharmacists (DP, KB) reviewed all medications reported and deleted those with indeterminate names, non-medications (e.g., amino acid supplements and herbal products) and non-regular over-the-counter medications (e.g., paracetamol, pseudoephedrine). Medication trade names were changed to generic names. Where a combination product was used, the component medications are reported individually. A senior hospital pharmacist (ST) then separated all medications into relevant major and minor medication classifications: cardiovascular, endocrine, neurological, psychotropic, respiratory or 'other' types of medication.

The primary outcome measure was the proportion of subjects in each group who regularly took at least one medication from a major medication classification. This allowed comparisons of the nature of the medications taken by the three subject groups (active comorbid divers, deceased divers and deceased snorkellers). Not all medications are detailed within this report; the focus being on those most relevant to diver safety (e.g., medications for ischaemic heart disease, epilepsy).

No *a priori* sample size calculation was undertaken as all cases who responded to the DAN AP survey and all scuba- and snorkelling-related deaths were included. The data are reported descriptively as absolute numbers (with percentages) and means (with standard deviations). Comparison of proportions and means employed the Chi-square and analysis of variance tests, respectively. SPSS for Windows statistical software (version 26.0, SPSS Inc., Chicago, Illinois, USA) was employed for all statistical analyses. The level of significance assumed was 0.05.

Results

Survey data on 268 active comorbid divers were available and there were 126 and 175 cases related to scuba diving and snorkelling fatalities, respectively. The mean age and gender mix of the three groups differed significantly ($P < 0.001$, Table 1). Overall, the deceased divers were

Table 1
Subject demographics and regular medication use

Parameter	Active comorbid divers *n* = 268	Deceased divers *n* = 126	Deceased snorkellers *n* = 175	*P*
Age, years mean (SD)	52.5 (12.1)	44.5 (12.0)	48.9 (18.1)	< 0.001
Males, *n* (%)	187 (70.0)	99 (78.6)	157 (89.7)	< 0.001
Takes one or more regular medications *n* (%)	155 (57.8)	36 (28.6)	39 (22.3)	< 0.001

Table 2

Absolute numbers of medications taken by the subject groups. COPD – chronic obstructive pulmonary disease; *Only if the medication was purely for epilepsy, i.e., phenytoin. Medications that had indications other than epilepsy were not included in this subclassification. #lithium (n = 3, one in each subject group), diazepam (two), nitrazepam (one), temazepam (one), clonazepam (one), alprazolam (one), dexamphetamine (one in the deceased diver group), bupropion (one), methylphenidate (one in the active group), melatonin (one)

Medication classification	Total number of medications taken by subject group (rate of use per subject)		
	Active comorbid divers n = 268	Deceased divers n = 126	Deceased snorkellers n = 175
Cardiovascular	209 (0.78)	25 (0.20)	56 (0.32)
Antihypertensives	143	14	24
Medications for dyslipidaemia	52	6	13
Medications for angina	1	1	8
Medications for heart failure	4	1	3
Other	9	3	8
Endocrine	46 (0.17)	3 (0.02)	5 (0.03)
Medications for diabetes	37	2	3
Other	9	1	2
Neurological	3 (0.01)	4 (0.03)	5 (0.03)
Antiepileptics*	0	1	0
Other	3	3	5
Psychotropic	11 (0.04)	14 (0.11)	10 (0.06)
Antidepressants	7	8	4
Antipsychotics	0	1	2
Other#	4	5	4
Respiratory	16 (0.06)	7 (0.06)	2 (0.01)
Medications for asthma or COPD	16	6	2
Other	0	1	0
Other	56 (0.21)	37 (0.29)	34 (0.19)
Total number of medications	341 (1.27)	90 (0.7)	112 (0.6)

younger than the active comorbid divers and deceased snorkellers were almost all male.

The use of regular medications differed significantly across the groups ($P < 0.001$, Table 1). More than one half of active comorbid divers took at least one regular medication, a proportion more than twice that documented for the deceased divers and snorkellers. A total of 161 different medication entities were taken by all groups combined, with active comorbid divers taking the greatest variety of these medications.

The 268 active comorbid divers took a total of 341 medications, whilst the 126 deceased divers took 90 medications and the 175 deceased snorkellers took 112 medications: rates of 1.27, 0.71 and 0.64 medications per subject, respectively ($P < 0.001$, Table 2). Approximately one half of medications taken by the groups combined (290, 53.4%) were for cardiovascular conditions with the active comorbid divers accounting for the large majority of these. Approximately one tenth of medications were for endocrine conditions and, again, most were taken by the active comorbid divers. The rate of psychotropic medication use was greatest amongst the deceased divers at 0.11 medications per subject. The numbers of respiratory medications were quite low although a considerable number of asthma medications were taken by the active comorbid divers.

The nature of the medications taken by the groups differed significantly ($P < 0.001$). Table 3 describes the number and percentage of all subjects in each group who took medications in major and minor medication classifications. For example, 16 (12.7%) of the 126 deceased divers took at least one cardiovascular medication. More than one quarter (28.3%) of all subjects took at least one cardiovascular medication, with the greatest proportion (44.4%) in the active comorbid

Table 3

Absolute numbers (%) of subjects who take one (or more) medication from each of the medication groups and subgroups. *Five snorkellers were known to be taking medications. However, the nature of these medications is not known. Hence, the number (%) of snorkellers taking medications is underestimated. #Only if the medication was purely for epilepsy i.e., phenytoin. Medications that had indications other than epilepsy were not included in this subclassification

Medication classification	Numbers (%) of subjects who take one or more medications		
	Active comorbid divers *n* = 268	Deceased divers *n* = 126	Deceased snorkellers *n* = 175*
Cardiovascular	119 (44.4)	16 (12.7)	26 (14.9)
Antihypertensives	96	14	17
Medications for dyslipidaemia	52	5	10
Medications for angina	1	1	7
Medications for heart failure	3	1	3
Other	3	1	1
Endocrine	32 (11.9)	2 (1.6)	4 (2.3)
Medications for diabetes	23	1	2
Other	10	1	2
Neurological	2 (0.7)	4 (3.2)	3 (1.7)
Antiepileptics#	0	1	0
Other	2	3	3
Psychotropic	8 (3.0)	12 (9.5)	6 (3.4)
Antidepressants	7	9	4
Antipsychotics	0	1	1
Other	4	4	4
Respiratory	13 (4.9)	5 (4.0)	2 (1.1)
Medications for asthma or COPD	13	5	2
Other	0	1	0
Other	37 (13.8)	19 (15.1)	26 (14.9)

diver group. This group also had a substantially greater proportion of subjects who took an endocrine medication, the majority of which were for diabetes.

The proportion of subjects who took an ACE-I was greatest in the active comorbid diver group compared to those who were deceased. These medications were taken by 15.7%, 3.2% and 4.0% of active comorbid divers, deceased divers and deceased snorkellers, respectively. The proportion of subjects who took beta-blockers was similar across all groups. These medications were taken by 4.5%, 1.6% and 2.3% of subjects, respectively.

There was an excess of psychotropic medication use within the deceased diver group. Almost one tenth of subjects in this group took one or more psychotropic medications, a proportion approximately three times greater than that of the active comorbid divers and the deceased snorkellers ($P = 0.01$).

Discussion

This study has found that many scuba divers and snorkellers take regular medications for a range of medical comorbidities. This is consistent with the findings of a 2000 survey of 709 active scuba divers in Australia and the United States (US).[12] However, substantially more active comorbid divers in our study took a medication (57.8%) than divers from Australia (15.6%) or the US (22.8%) in the 2000 survey. The reasons for this likely relate to the fact that our survey explicitly included divers with a declared medical condition. There is also the possibility of prevarication bias in the 2000 survey.[12] At that time, diving with some comorbidities was less acceptable (e.g., cardiac disease) and some medications may not have been disclosed.

Overall, a wide range of medications was taken by all subjects – 161 different medication entities in total. Of these, the active comorbid divers took a significantly greater range than the deceased subjects. This is likely related to the greater proportion of active divers who took any medications and consistent with their known major pre-existing condition profiles.[4,5,10,11]

Cardiovascular medications, especially those for hypertension and hypercholesterolaemia, were the most common medications taken in each of the subject groups. Cardiovascular medications were particularly common in the active comorbid diver group, taken by almost one half of subjects. Relatively few of the deceased subjects took ACE-I and beta-blocker medications compared to the active comorbid diver group. Hence, despite concerns about

the effects of these medications in the diving environment (particularly beta-blockers),[16] these concerns do not appear to be supported by the patterns of medication use in this study.

It is also notable that a sizable proportion of active divers took an endocrine medication, mainly for diabetes. This proportion is substantially higher than for the deceased subject groups. Once again, these findings likely reflect the pre-existing medical conditions and the older age of the active comorbid divers.

One important finding was that almost one tenth of deceased divers took a psychotropic medication. This proportion is less than that of the general Australian population (16.3%) during 2013–2014,[22] a similar period to the active comorbid diver survey.[10] However, it is almost three times that of the active comorbid divers and deceased snorkellers. The psychotropic medications were mostly antidepressants but also included anxiolytics/sedatives (mainly benzodiazepines) and antipsychotics. In 2013–2014, 11.5% and 1.9% of Australians took antidepressants and antipsychotics, respectively.[22] The use of diazepam, clonazepam and alprazolam hints that these subjects were treated for anxiety. However, medications classed as antidepressants may be used for a range of indications other than depression, including chronic pain syndromes. It is not possible from the data available to comment upon the specific indication for which the antidepressants were prescribed. The use of dexamphetamine and methylphenidate is likely to have been used for attention deficit hyperactivity disorder.

In Australia over the past few decades, there has been a large increase in the use of psychotropic drugs, most notably antidepressants.[23] However, the reasons for this apparent excess of psychotropic medication use in the deceased diver group are unclear. This does, however, raise the possibility that the use of these medications may have been associated with the diving deaths. However, given the available information, it is not possible to attribute the deaths to the divers' underlying co-morbidities, the medications themselves or any other factor.

There is evidence that the hyperbaric environment can affect the mental capacity of subjects taking dimenhydrinate (an antihistamine).[9] Also, there are suggestions that some antidepressants may increase the risk of nitrogen narcosis and induce seizures.[15] Presently, however, there is little robust evidence to indicate that this environment affects the actions of psychotropic medications to an extent that puts the diver at significantly greater risk.[14,15] A more likely possibility is that a psychiatric comorbidity may render the diver less fit to dive by affecting cognition, emotion and behaviour. However, it is not known if the deceased divers on psychotropic medications were more prone to poor decision-making, panic attacks or other aberrant behaviour that could have contributed to their diving incident. It has been reported that individuals with raised anxiety trait levels are more likely to experience anxiety and panic in stressful diving situations.[24] This is thought to relate to a dysregulation of the hypothalamic–pituitary–adrenal axis that may initiate a strong response to a relatively mild stress. Importantly, it has also been reported that divers with mental health issues do not consistently declare their condition or psychotropic medication use on diver certification forms.[25] Finally, as the majority of psychotropic medications were antidepressants, it is possible that some divers did not have their depression well-controlled, if this was the indication for which the antidepressants were prescribed. This raises the possibility, albeit unlikely, that one or more of the deaths was intentional though there is no clear evidence to suggest that this was the case. Although there are occasional reports of diver-related deaths through suicide, other suicide methods are much more common and usually do not place other individuals at risk, as a diving suicide may do for the diving buddy.[26]

Small but important proportions of subjects were taking medications for asthma, once thought to be an absolute contra-indication to scuba diving.[5] Over time, asthma has moved from an absolute to a relative contra-indication to scuba diving.[27,28] It is now recognised that, if this condition is well-controlled, the theoretical risk of diving with asthma is mitigated.[28] It is hoped that the divers on asthma medications are taking them to ensure their management is optimised.

The retrospective design and relatively small sample sizes of this study do not allow definitive conclusions. Some of the suggested reasons for the findings can, therefore, only be conjecture. We recommend that large, similar studies of medication use by active and deceased divers are undertaken. In particular, the apparent excess of psychotropic medications among deceased divers needs to be further investigated. If this association is supported by future research, this will have implications for fitness to dive and may support psychological testing as part of a diving medical examination. While this may be advisable, it has been reported that the diving medical physician may have neither the time nor the experience to conduct an adequate psychological assessment.[24] One potential solution may be thorough screening by means of an extensive questionnaire with attention to psychiatric disorders and psychotropic medication use. If this suggests doubt about the diver's fitness to dive then referral to a psychiatrist with an understanding of diving medicine may be indicated.

This study has other limitations. The 2013 survey[10] was only sent to divers with a declared medical condition which almost certainly explains the higher prevalence of overall medication use amongst this group. Non-response to the survey may have resulted in selection bias and the self-report of medication use may have been affected by recall or prevarication bias. Selection bias is unlikely among the deceased diver and snorkeller groups as all subjects were included. The medication data relating to the deceased subjects will be an underestimate. The use of some medications by the active comorbid divers may also

have been an underestimation if the use of medications was not disclosed during diving medicals or the divers survey. In a small number of cases, it was noted that medications were taken but the actual names were not available. Also, inaccuracies may be present in their medication lists as they were obtained by subject self-report and not verified by another source. Some medications taken have several, quite different, indications. For example, carbamazepine can be used for epilepsy, neuropathic pain, mania and bipolar affective disorders. Given the retrospective nature of this study, the exact indication for a medication was often not known. When this occurred, we assigned the indication to the less serious condition. For example, if there was no medical history of epilepsy, the use of carbamazepine was assumed to be used for neuropathic pain. Hence, the prevalence of some comorbidities will be an underestimation.

Conclusions

In this study, the use of medications among active comorbid divers, deceased divers and snorkellers was common. The active comorbid divers differed from the two deceased groups in that they used significantly more medications. This likely reflects their declared medical conditions and older age. Notwithstanding these characteristics, the active comorbid divers appear to be diving relatively safely with conditions once thought to be contraindications to scuba diving. This suggests that there are multiple influences on mortality in diving beyond medical comorbidities. The deceased divers took more psychotropic medications. It is not clear if these medications themselves contributed to their deaths. More likely is the possibility that their underlying psychological or psychiatric conditions rendered them more at risk in the diving environment. If these findings are replicated in future studies, there may be sufficient evidence to consider the incorporation of psychological testing into diving medical examinations.

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Efficacy and safety of hyperbaric oxygen treatment in SARS-COV-2 (COVID-19) pneumonia: a systematic review

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Key words
Hyperbaric medicine; Hypoxia; Infection

Abstract
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Introduction: The need for intubation and mechanical ventilation among COVID-19 patients is associated with high mortality rates and places a substantial burden on the healthcare system. There is a strong pathophysiological rationale suggesting that hyperbaric oxygen treatment (HBOT), a low-risk and non-invasive treatment, may be beneficial for COVID-19 patients. This systematic review aimed to explore the potential effectiveness and safety of HBOT for treating patients with COVID-19.

Methods: Medline, Embase, Scopus, and Google Scholar were searched from December 2019 to February 2021, without language restrictions. The grey literature was searched via an internet search engine and targeted website and database searches. Reference lists of included studies were searched. Independent reviewers assessed studies for eligibility and extracted data, with disagreements resolved by consensus or a third reviewer. Risk of bias was assessed using the Newcastle Ottawa Scale. Data were summarised descriptively.

Results: Six publications (one cohort study, five case reports/series) met the inclusion criteria with a total of 37 hypoxaemic COVID-19 patients treated with HBOT. Of these 37 patients, the need for intubation and mechanical ventilation and in-hospital survival were assessed for 26 patients across three studies. Of these 26 patients, intubation and mechanical ventilation were not required for 24, and 23 patients survived. No serious adverse events of HBOT in COVID-19 patients were reported. No randomised trials have been published.

Conclusions: Limited and weak evidence from non-randomised studies including one propensity-matched cohort study suggests HBOT is safe and may be a promising intervention to optimise treatment and outcomes in hypoxaemic COVID-19 patients. Randomised controlled studies are urgently needed.

Introduction

The current SARS-CoV-2 (COVID-19) viral pandemic has infected over 143 million individuals, with over 3.1 million deaths worldwide as of April 21, 2021.[1] Approximately 15 to 20% of patients present with hypoxaemic respiratory failure requiring oxygen supplementation.[2] Although outcomes may vary depending on factors such as age, comorbidities and initial oxygen requirements,[3,4] overall one in five of these patients die in hospital.[5–7] Among hospitalised hypoxaemic COVID-19 patients, one in four require intensive care (ICU) admission and among these, 60% require intubation and 30% die in-hospital.[3,5,8,9] Mechanical ventilation and ICU admission are limited resources, placing a substantial burden on the healthcare system.

As the COVID-19 pandemic continues to evolve, there remains a need for a low risk and non-invasive intervention that can both prevent the adverse progression of moderate cases and improve survival in severe cases. Hyperbaric oxygen treatment (HBOT) is one potential solution. HBOT is defined as breathing 100% oxygen at a pressure > 142 kPa (1.4 atmospheres absolute [atm abs]).[10] HBOT is a well-established and safe[11] method to increase tissue

oxygen delivery up to 10–20 fold at 203 to 304 kPa (2–3 atm abs) pressure.[12] HBOT is currently approved by the US Food and Drug Administration and Health Canada for 14 indications for both elective (e.g., late radiation tissue injury, non-healing chronic wounds) and urgent conditions (e.g., carbon monoxide poisoning, decompression sickness, gas embolism).[10]

The clinical use of HBOT for patients with severe COVID-19 is supported by physiological and preclinical rationales.[13] First, hyper-oxygenation of arterial blood with oxygen dissolved in plasma corrects tissue oxygen debt. Second, HBOT has a strong anti-inflammatory effect.[14,15] Indeed, preclinical and clinical studies show that HBOT has a strong immunomodulatory effect regulating the inflammatory response through several pathways.[14,15] HBOT stimulates both the humoral and cellular immune response, resulting in decreasing pro-inflammatory cytokines while increasing anti-inflammatory cytokines.[15] Intervening early to limit the increase of plasma IL-6 may be beneficial since elevated levels of IL-6 are independently associated with mortality for COVID-19 patients.[16] Furthermore, intermittent hyperoxia (i.e., HBOT) promotes stem cell mobilization and cytokine expression.[17] Stem cells represent another pathway through which HBOT may have positive effects on COVID-19 patients. Mesenchymal stem cells (MSCs) are known to have strong anti-inflammatory and immunomodulatory properties.[18] Therefore, MSCs may contribute to preventing overreaction of the immune system, referred to as the cytokine storm, by limiting pro-inflammatory cytokines and increasing anti-inflammatory cytokines.[19] Finally, HBOT may have a direct viricidal effect on SARS-CoV-2 similar to the direct viricidal action that has been demonstrated in preclinical research in other enveloped viruses.[20]

Despite the potential for HBOT to reduce the rate of invasive mechanical ventilation and possibly mortality for COVID-19 patients, its effectiveness and safety has yet to be quantified. As the number of new COVID-19 cases continues to rise,[1] a systematic review of the efficacy and safety of HBOT is urgently needed. Results will inform COVID-19 research and practice in order to optimise recovery for patients and reduce the burden of the pandemic on the healthcare system as quickly as possible.

We aimed to systematically summarise the existing literature on the clinical effect of HBOT for COVID-19 patients to inform future clinical trials and practice decisions.

Methods

PROTOCOL

This review was planned and conducted according to the Cochrane Handbook for Systematic Reviews of Interventions and reported in adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist.[21] The protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO, CRD 42020209933).

Box 1
Study eligibility criteria

Population: Patients of any age, who were diagnosed with COVID-19 (either positive, confirmed with clinical or biological tests, or suspected). A sensitivity analysis was conducted to measure the effect of HBOT on COVID-19 patients for whom there was diagnostic proof by reverse transcriptase polymerase chain reaction.

Intervention: Hyperbaric oxygen treatment (HBOT) for clinical use is defined as breathing 100% oxygen at a pressure > 142 kPa (1.4 atmospheres absolute).[6] HBOT was administered with the intention of treating COVID-19.

Control: Usual treatment or no treatment/comparator (for case series, case reports, or cohorts).

Outcome: At least one clinical outcome (e.g., mortality; need for intubation and mechanical ventilation).

Design: Randomised or non-randomised trial, case control, cross-sectional, case series, case reports.

Language of publication: Any language.

Date of publication: Since December 2019, when the first human case of COVID-19 was reported.

ELIGIBILITY CRITERIA

Eligibility criteria were pre-specified as described in Box 1.

Articles were included if they involved patients of any age undergoing at least one HBOT session with the intention of treating patients with confirmed positive or suspected COVID-19. Studies involving patients who received HBOT for other purposes while also having confirmed or suspected COVID-19 were not included. To be eligible for inclusion, studies had to assess at least one clinical outcome measured at any time point after HBOT was initiated. Of primary interest were the clinical outcomes of mortality and the need for intubation and mechanical ventilation. In addition to clinical outcomes, studies could also assess biological outcomes (e.g., inflammation markers), imaging outcomes (e.g., chest computed tomography [CT]), cost outcomes (e.g., length of stay), and safety outcomes (any adverse events related to HBOT).

In the context of a new disease leading to a pandemic with no definitive cure, we elected to include all types of study designs, such as randomised and non-randomised trials, case-control studies, cross-sectional studies, case series and case reports. Both peer-reviewed studies and pre-prints were eligible for inclusion. We did not impose language restrictions. We excluded editorials and conference abstracts.

SEARCH STRATEGY AND INFORMATION SOURCES

The search strategy was developed by an experienced information specialist (LS) in close collaboration with the research team (Appendix 1*). It was then reviewed by a second information specialist, following the Peer Review of Electronic Search Strategies (PRESS) guidelines.[22] The databases MEDLINE via Ovid, EMBASE via Ovid, Scopus, and Google Scholar were searched without language restrictions from 01 December 2019 to 04 February 2021. References not published in English or French were translated using DeepL Translator (DeepL GmbH, Cologne, Germany). The reference lists of included studies were also searched in addition to related reviews. Our systematic grey literature (i.e., difficult to locate/unpublished) search strategy was developed by the co-author team and consisted of three parts: internet search engine (using anonymous browser to avoid geographical bias); targeted website searching of hyperbaric medicine organisations (e.g., Undersea and Hyberbaric Medical Society, International Association of Francophone Hyperbaric Centres); and targeted grey literature database searching (e.g., World Health Organization, Centres for Disease Control and Prevention, clinicaltrials.gov, medRxiv, bioRxiv, LitCovid, COVID-END). We also consulted content experts and the authors' personal files to ensure literature saturation.

STUDY SELECTION AND DATA EXTRACTION

Following removal of duplicates and a pilot test of a screening form, identified studies were screened using DistillerSR (Evidence Partners, Ottawa, Canada), a systematic review software. Two independent reviewers (RK, GD) assessed titles and abstracts for eligibility. The full-text of articles of included studies and those deemed 'unclear' were subsequently screened. Screening for inclusion at each level was always conducted in duplicate, with disagreements resolved by consensus or involvement of a third reviewer as needed (SB).

A data extraction form was developed and used by the two independent reviewers (RK, GD) to extract relevant information with Microsoft Excel. Extracted data included publication details (e.g., first author name, year of publication, country of data collection, funding, trial registration), study characteristics (e.g., study design, sample size, inclusion/exclusion criteria), patient demographics, intervention and comparator details, the type of hyperbaric chamber, and the effect of intervention on reported clinical outcomes. Discrepancies in extraction were resolved by a third reviewer (SB).

RISK OF BIAS

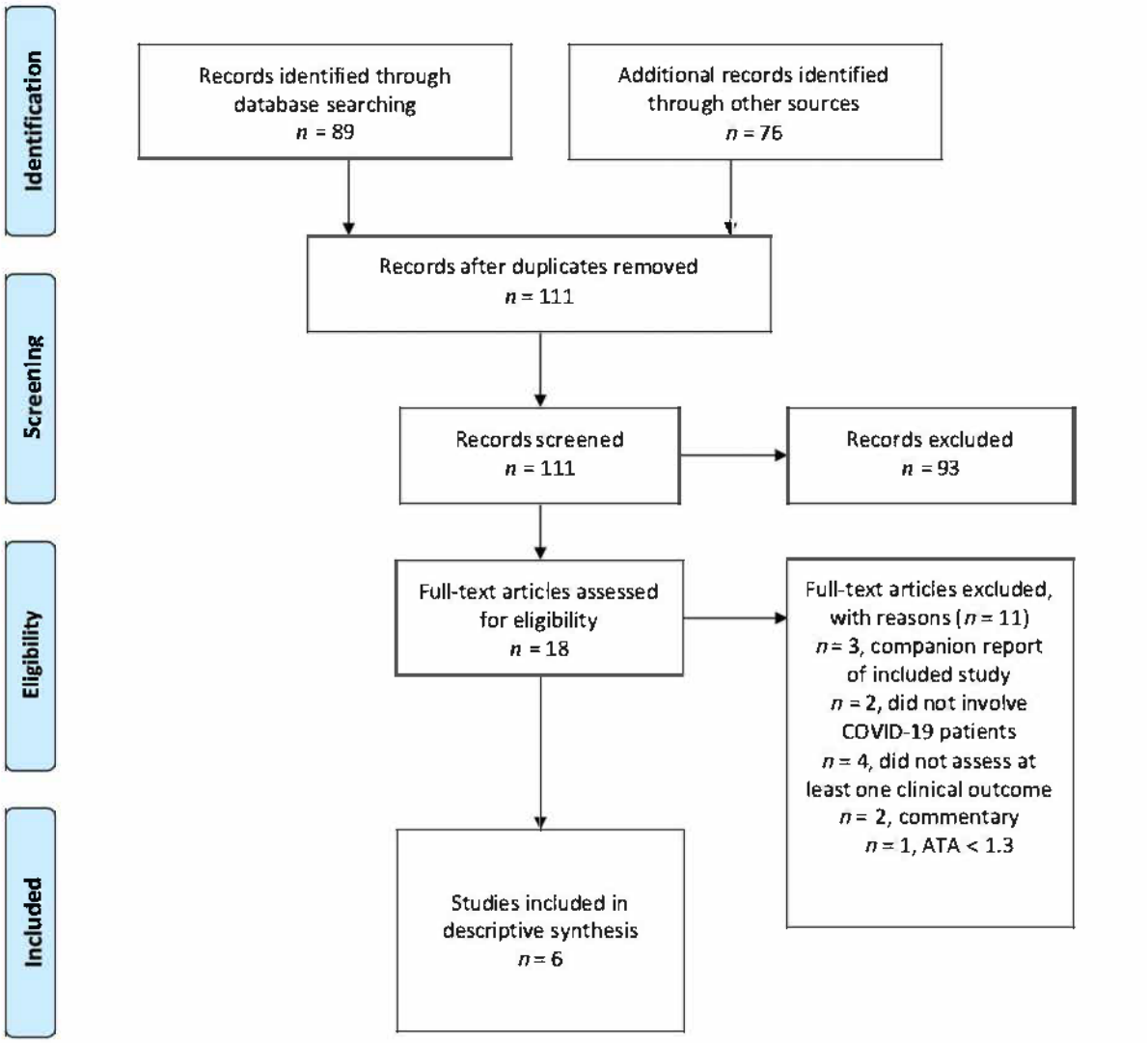
An estimate of the risk of bias was not performed for case series data given the inherent limitations and high possibility of bias for these types of studies. For included comparative cohort studies, two independent reviewers (RK, GD) assessed risk of bias using the Newcastle Ottawa Scale.[23] The Newcastle Ottawa Scale can be used to assess case and cohort studies across three domains: selection, comparability, and outcome/exposure. Each domain is comprised of a series of questions and stars are given according to each item. A maximum of four stars can be given in the Selection and Outcome/exposure domains and a maximum of two stars can be given in the Comparability domain. The star system can then be converted to the Agency for Health Research and Quality standards of good, fair, and poor quality. Good quality is assigned to studies with at least three stars in the Selection domain, one star in the Comparability domain and two stars in the Outcome/exposure domain. Fair quality is assigned to studies with two stars in the Selection domain, at least one star in the Comparability domain and at least two stars in the Outcome/exposure domain. Poor quality is assigned to studies with zero or one stars across the domains. A pilot test was conducted with one article prior to risk of bias assessment.

ASSESSMENT OF THE CERTAINTY OF EVIDENCE

The certainty of the evidence for included comparative studies was assessed using the GRADE approach,

Footnote: * Appendix 1 is available on DHM Journal's website: https://www.dhmjournal.com/index.php/journals?id=191

Figure 1
PRISMA flow diagram



which considers five domains: risk of bias, indirectness, inconsistency, imprecision and publication bias.[24] Based on the grading of these domains, the certainty of the evidence was rated as high, moderate, low or very low.

DATA SYNTHESIS

A meta-analysis was planned for our pre-specified primary and secondary outcomes but was not conducted based on the heterogeneity of the included studies. Therefore we provide a descriptive synthesis of the current literature.

Results

The literature search yielded 165 studies. After removal of duplicates, 111 studies were assessed for eligibility (Figure 1). The majority of these studies either did not involve the use of HBOT to treat COVID-19 patients, did not assess at least one clinical patient outcome, or were not an original study or case report (e.g., commentaries, position statements). Subsequently, six studies met the inclusion criteria and were included in this systematic review.

STUDY AND PATIENT CHARACTERISTICS

Details of included study and patient characteristics are provided in Table 1. Three studies were case series[25–27] and two studies involved case reports of one[28] or two[29] patients. One study was a cohort design with propensity-matched controls, where 20 COVID-19 patients were treated with HBOT and compared to 60 similar patients (matched based on age, sex, body mass index, coronary artery disease, troponin, D-dimer, hospital day, and oxygen requirement) from the same hospital who received usual care (no HBOT).[30]

Table 1

Study characteristics; all studies were single centre. ARDS – acute respiratory distress syndrome; NR – not reported; P/F ratio – PaO_2/FiO_2, where PaO_2 is the arterial oxygen partial pressure and FiO_2 is the fraction of inhaled oxygen); SpO_2 – peripheral oxygen saturation

Study	Study design	Inclusion criteria	Exclusions	Intervention
Chen[25] China	Case series, *n* = 5	Progressive hypoxaemia, moderate-severe ARDS, laboratory confirmed COVID-19	NR	Multiplace 203 kPa for one patient, 162 kPa for four patients, 60–90 min. Mean five HBOT sessions (range 3–8)
Gorenstein[30] USA	Cohort study with controls chosen from patients treated in the same hospital and time period using propensity score matching, *n* = 80 (20 intervention; 60 control)	Age ≥ 18, laboratory confirmed COVID-19, SaO_2 < 93% on air	Pregnancy, pneumothorax, positive troponin	Monoplace 203 kPa, 90 min per day, once daily for five days
Guo[29] China	Case reports, *n* = 2	Confirmed COVID-19, and one of: shortness of breath; respiratory rate ≥ 30 breaths·min^{-1}; SpO_2 ≤ 93% at rest; and P/F ratio ≤ 300 mmHg	Pneumothorax, pulmonary bullae	Monoplace, 152 kPa, 60 min, once daily for seven days
Qian[26] China	Prospective case series, *n* = 4	Progressive dyspnoea, lung CT lesion area > 30%, SpO_2 < 90% on air, clear consciousness, able to communicate in words, minimal education to junior high	Pneumothorax, pulmonary bullae	Portable monoplace chamber; 152 kPa, 90 min, once daily for seven days
Thibodeaux[27] USA	Retrospective case series, *n* = 5	Impending respiratory failure, imminent intubation	NR	Type of chamber not reported. 203 kPa, 90 min. Mean five HBOT sessions (range 1–6)
Zhong[28] China	Case report, *n* = 1	Critically ill with pneumonia and tracheal intubation, confirmed COVID-19 from tracheal aspirate	NR	Multiplace chamber, 162–182 kPa for 70–100 min. Four HBOT sessions

Table 2
Patient demographic characteristics; #60 controls and 20 patients treated with HBOT; COPD – chronic obstructive pulmonary disease; HBOT – hyperbaric oxygen treatment; NR – not reported

Study	*n*	Female *n*	Age (years)	Ethnicity	Comorbidities
Chen[25]	5	1	Mean 47 Range 24–69	Chinese: 5	Hypertension: 1 Cardiovascular disease: 1
Gorenstein[30]	80#	7	HBOT: Median 58 Range 30–79 Control: Median 62 Range 24–80	White: 23 Black: 13 Asian: 7 Other: 37	Hypertension: 40 (50%) Diabetes: 24 (30%) Cardiovascular disease: 8 (10%) COPD: 4 (5%)
Guo[29]	2	0	57 and 64	Chinese: 2	Hypertension: 1 Diabetes: 1 Cardiovascular disease: 1
Qian[26]	4	0	Range 56–67	Chinese: 4	NR
Thibodeaux[27]	5	4	Median 48 Range 39–63	White: 2 Black: 3	Obese: 4 Hypertension: 4 Diabetes: 3
Zhong[28]	1	0	87	Chinese	Cardiovascular disease COPD

Across the six included studies, 37 participants were treated with HBOT for COVID-19. All the patients treated with HBOT were hypoxaemic in room air and required (normobaric) oxygen supplementation. The COVID-19 cases treated by HBOT were from the United States of America (two publications, 25 patients) and China (four publications, 12 patients).

All patients treated with HBOT were adults (ranging from 24 to 87 years old) and 12 patients were female (32%) (Table 2). Only one study included a control group with no HBOT, and was a propensity matched design.[30] Only one case was intubated and mechanically ventilated while being treated with HBOT.[28]

HBOT ranged from one to seven sessions, each session lasting between 60 minutes[29] and 100 minutes[28] at a pressure between 152[26,29] to 203 kPa[25,27,30] (1.5–2.0 atm abs).

EFFECTIVENESS OF HBOT FOR COVID-19

The seven publications included clinical, biological and imaging outcomes. Cost outcomes were not reported by any of the studies. Clinical outcomes were the most frequently reported (six studies, 37 patients), followed by biological (5 studies, 17 patients), and imaging outcomes (4 studies, 11 patients). Detailed outcomes of included studies are provided in Table 3 and Table 4. Improvements in clinical (e.g., survival), biological (e.g., lymphocyte count, renal function) and imaging (e.g., chest CT) outcomes were observed for the majority of the 37 hypoxaemic COVID-19 patients across all studies (Table 3).

Of the 37 included hypoxaemic COVID-19 patients treated with HBOT, the need for mechanical ventilation and in-hospital survival was reported for 26 patients across three studies (Table 4). Of these 26 patients, 24 did not require mechanical ventilation and 23 survived. Improvements in oxygen saturation (17 patients, 5 studies), respiratory rate (7 patients, 2 studies), walking distance (4 patients, 1 study), and shortness of breath (6 patients, 2 studies) were also observed (Table 4).

RISK OF BIAS AND GRADE ASSESSMENT

There was only one included comparative study for which risk of bias assessment and GRADE assessment could be conducted.[30] This study was deemed to be of good quality with moderate certainty in the evidence (Table 5).

Discussion

This systematic review found six studies reporting on 37 hypoxaemic COVID-19 patients who were treated with HBOT. Available data from the included cohort and case studies suggest that the use of HBOT to treat COVID-19 patients may be promising and urgently requires randomised controlled trials (RCTs). These early data show that HBOT may be useful for preventing deterioration requiring intubation and mechanical ventilation in COVID-19 patients. However, since many admitted hypoxaemic COVID-19 patients will not require intubation and will survive, studies with comparative data are paramount. In addition, no serious adverse events were reported by any of the included studies. However, all studies were of poor quality and the certainty of the evidence was low or very low, with the exception

Table 3

Effect of HBOT on COVID-19 patient outcomes; *results that were reported as significant at $P < 0.05$; #60 controls and 20 patients treated with HBOT; bpm – breaths per minute; HCO_3^- – bicarbonate; HBOT – hyperbaric oxygen treatment; NR – not reported; P/F ratio – PaO_2/FiO_2, where PaO_2 is the arterial oxygen partial pressure and FiO_2 is the fraction of inhaled oxygen); SaO_2 – arterial oxygen saturation; SpO_2 – peripheral oxygen saturation

Study	*n*	Timing of outcome measurement	Clinical outcomes Data are mean (SD)	Biological outcomes Data are mean (SD)	Imaging outcomes	Safety outcomes
Chen[25]	5	Assessed before and after course of HBOT (average of five sessions per patient)	**SpO_2 improved:** 73 (6) to 94 (2)%*	PaO_2 and SaO_2 increased* Lymphocyte count increased: 0.61(0.35) to 1.09 (0.24) x$10^9 \cdot L^{-1}$* C-reactive protein levels decreased: data NR D-dimer decreased: data NR* Fibrinogen decreased: data NR*	CT improved (qualitatively)	NR
Gorenstein[30]	80#	Assessed at end of study (patients received up to five daily treatments as long as supplemental oxygen still required)	**Inpatient mortality:** HBOT: two (10%) died, none remained hospitalised at end study. Controls: 13 (22%) died, three (5%) remained hospitalised at end study. **Mechanical ventilation:** HBOT: 2 (10%) Controls: 18 (30%) **Adjusted hazard ratios:** Inpatient mortality = 0.37 ($P = 0.14$); Mechanical ventilation = 0.26*	N/A	N/A	Claustrophobia, ear pain (n = NR) Hypoxic arrest in unclear circumstances after transferring to the floor (n = 1)
Guo[29]	2	Assessed over 7-day course of HBOT	Dyspnoea eliminated immediately after the first HBOT session Respiratory rate decreased daily; no need for mechanical ventilation $SpO_2 > 93\%$ after the first session and continued to improve	D-dimers reduced Lymphocyte counts improved PaO_2, P/F ratio, HCO_3^-, lactate improved Liver function (cholinesterase) improved Data NR for any outcomes	CT pulmonary inflammation gradually improved	No adverse effects

Table 3 continued.

Thibodeaux[27]	5	Assessed before and after course of HBOT (average of 5 treatments per patient [range: 1–6])	SpO_2 improved: 96 (3) to 96 (1)% All patients recovered without need for mechanical ventilation Respiratory rate decreased: 35.4 (8.5) to 28 (7.6) bpm	Inflammatory markers decreased (reported for 1 patient, not reported for 4 patients)	N/A	No adverse effects
Qian[26]	4	Assessed before and one day after 7-day course of HBOT	**SpO_2 improved:** 86 (5) to 92 (4)%* **Six-minute walk distance improved:** 272 (62) to 346 (43) m* Dyspnoea improved	Blood gas analysis indexes improved	CT resolution of inflammation to different degrees	NR
Zhong[28]	1	Assessed before and after course of HBOT (4 sessions)	Oxygenation improved Patient was eventually extubated	CO_2 reduced Coagulation normalised Kidney function improved	N/A	NR

of the one comparative study.[30] While a few RCTs were registered, none were published.

Although conclusions are limited by study quality and risk of bias, the positive clinical outcomes observed by the included studies are supported by concordant biological and radiological data. Findings of effectiveness across multiple outcome categories are also supported by a compelling physiological rationale. While HBOT was first considered for treating hypoxaemic COVID-19 patients to quickly correct their tissue hypoxia, more evidence suggests that the immunomodulatory effect of HBOT may also be relevant.[14,15] COVID-19 is increasingly considered as an endothelial disease,[31,32] which provides a unifying pathophysiological picture. This endothelial dysfunction explains both the range of symptoms experienced by COVID-19 patients (e.g., thrombotic events, neurologic manifestations), and why patients with pre-existing impaired endothelial function (e.g., age, diabetes, cardiovascular disease) are also more at risk for severe COVID-19. Evidence suggests that endothelial cells contribute to the initiation and propagation of pneumonia by altering vessel barrier integrity, promoting a pro-coagulative state, and inducing vascular inflammation.[33] The anti-inflammatory effect of HBOT may counteract the inflammation of the endothelium caused by COVID-19 and prevent a cytokine storm leading to multi-organ dysfunction and death. Accordingly, positive findings for both safety and effectiveness across each of the included studies conducted in diverse locations, combined with the pathophysiological mechanisms, suggest an urgent need for rigorous RCTs to fully assess the effectiveness of HBOT for hypoxaemic patients.

There are currently eight registered RCTs that aim to test the effectiveness of HBOT as a treatment for COVID-19. Of these, two are completed (results not yet available),[34,35] two are recruiting,[36,37] and four are not yet recruiting.[38–41] This suggests the need for a living systematic review to continue to inform practice throughout the pandemic. Our present review represents an initial step toward this end. One of the strengths of our systematic review is its early summary of the current evidence for a safe non-invasive therapy that could potentially improve mortality and morbidity in severe COVID-19 patients. Given the pandemic context, patients and clinicians need to access current evidence with no delay. Our study may be helpful to clinicians, decision makers and patients to make an evidence-based decision when contemplating use of HBOT for hypoxaemic COVID-19 patients. Although the studies included in our review were mostly case series, this does not negate the potential of these studies to promote a broader understanding of COVID-19 treatments and outcomes. It may also assist clinicians in making a decision regarding the compassionate use of HBOT in the context of COVID-19 until results from RCTs are available.

It should be acknowledged that there may be more evidence that was not captured in this review. This may be due to the

Table 4
Clinical outcome summary of 37 COVID-19 patients treated with hyperbaric oxygen

Outcome	Patients assessed (*n*)	Patients improved (*n*)
Avoided mechanical ventilation	26	24
In-hospital survival	26	23
Oxygen saturation	17	17
Respiratory rate	7	7
Walking distance	4	4
Shortness of breath	6	6

Table 5
Risk of bias assessment using the Newcastle-Ottawa Scale. A maximum of 4 stars can be given in the Selection and Outcome/exposure domains and a maximum 2 stars can be given in the Comparability domain

	Newcastle Ottawa scale for risk of bias assessment				GRADE assessment
	Selection	Comparability	Outcome/ exposure	Overall quality assessment	Certainty of evidence
Gorenstein[30]	★★★★	★★	★★★	Good	Moderate

fast-moving nature of the pandemic, the delay of the peer-review system, indexation of publications in databases, and the possible publication of cases in non-peer-reviewed media. Only one study was of good quality with a moderate level of certainty in the evidence, and that study reported mortality and mechanical ventilation outcomes.

Finally, no cost data were reported in any of the included studies. However, if HBOT can prevent intubation, mechanical ventilation, and intensive care admission for hypoxaemic COVID-19 patients, then it is likely to be cost-effective. If the positive outcomes identified by our systematic review are confirmed by RCTs, the prompt use of mobile or portable chambers may be part of the solution to fight the current pandemic and avoid overwhelming the limited critical care resource at hospitals.

Conclusions

Limited and weak evidence suggests that HBOT may be a safe and promising intervention to improve COVID-19, including prevention of intubation and death in hypoxaemic COVID-19 patients. Studies were mostly of poor quality and the certainty of the evidence was low or very low. This systematic review supports the urgent need for a large-scale clinical trial to provide a rigorous level of evidence that could guide practice during the COVID-19 pandemic.

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Injuries in underwater rugby: a retrospective cross-sectional epidemiological study

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Key words
Aquatic sports; Breath-hold diving; Diving research; Epidemiology; Gender; Health Survey; Trauma

Abstract
(Meyer H-L, Minnemann F, Polan C, Burggraf M, Dudda M, Kauther MD. Injuries in underwater rugby: a retrospective cross-sectional epidemiological study. Diving and Hyperbaric Medicine. 2021 September 30;51(3):282–287. doi: 10.28920/dhm51.3.282-287. PMID: 34547779.)

Introduction: Underwater rugby (UWR) is a team sport which combines swimming sprints, apnoea diving, a good overview of the three-dimensional underwater space and wrestling for the ball.This was the first epidemiological study of UWR injuries in a large international collective.

Methods: A questionnaire containing 124 questions was distributed to 198 active UWR players and completed under the supervision of medical staff. Demographic data and information about injuries in ten different body regions were collected.

Results: Of the 198 respondents, 106 (53.5%) were male and 92 (46.5%) were female. On average, each UWR player suffered a median of 19.5 (IQR 44) injuries. Based on the exposure time, means of 37.7 (SD 90.0) injuries per 1000 playing hours per player and 9.9 (20.1) injuries per year were found. Significant injuries mainly occurred to the head region (45.7%). Bruises and sprains were observed more often than fractures and dislocations. Male athletes had a longer total injury break time (median 4.8 [IQR 10.5] days), than female athletes (4 [8.6] days). Female athletes had more injuries (median 20 [IQR 26.8]) than male athletes (18.5 [63]). The length of the injury-related break time increased with the rise in body mass index.

Conclusions: The risk of severe injury in UWR is low compared to other ball sports like water polo and rugby. UWR is played under water and the impact of tackles is lessened by the water. Further studies should record chronic injuries in UWR and establish measures to prevent injury.

Introduction

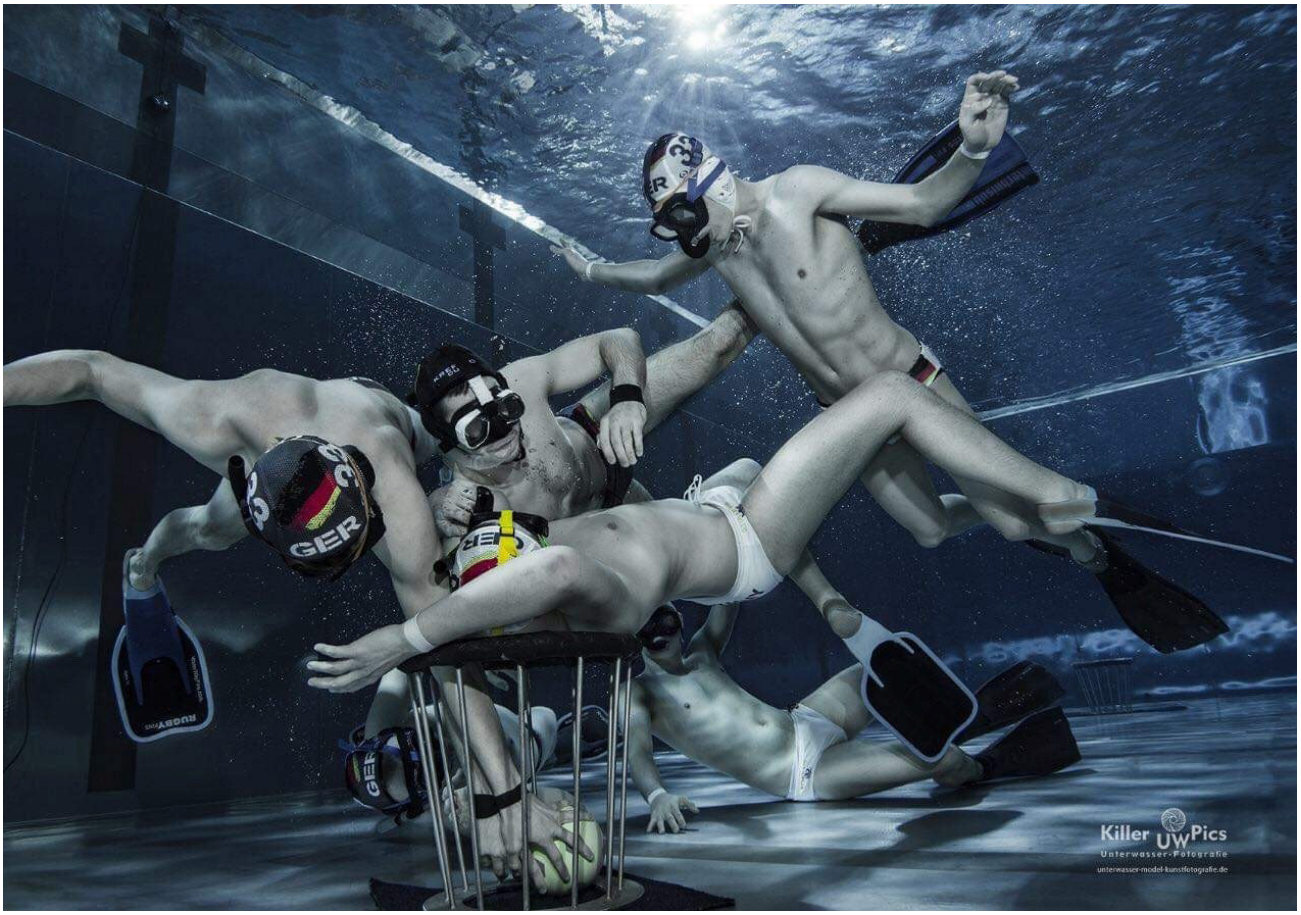
Germany is the birthplace of underwater rugby (UWR) which has been played there since the 1960s. International championships have been held regularly by the Confédération Mondiale des Activités Subaquatiques (CMAS) since the 1970s. There are now national championships in UWR in over 30 countries. World championships with men's and women's teams take place every four years. In addition to the European Championship, there is an annual cup of league winners, the Champions Cup. UWR is a team sport with a maximum of 15 players per team. The game takes place in the three-dimensional playing field of a swimming pool and lasts 30 minutes with two half-times of 15 minutes. To score a goal, the saltwater filled ball must be placed in the opponents' metal basket on the pool floor (Figure 1). UWR requires high endurance, strength and good apnoea training. But tactical sense, maneuverability and speed are also necessary, as correct positioning is crucial for a good passing game. A good overview of the three-dimensional underwater space is essential because members of the opposing team can attack from above or below. Depending on the game situation, the players dive for approximately 15 to 45 seconds in order to intervene again after surfacing to take a few breaths. Every player in possession of the ball may be attacked and may attack other players. Permitted tackles include holding on to arms and legs, scrambling for the ball or pushing the defender away. Attacks on players' equipment (swimwear, head caps with ear protection, diving masks and straps, snorkel and fins) are prohibited. Three referees supervise the game with horn signals that are clearly audible underwater.[1,2] So far, no studies on injury rates and patterns in UWR have been published. The aim of this study was to compile an epidemiological record of UWR-related injuries and overload damage.

Methods

This retrospective cross-sectional epidemiological study was carried out using a questionnaire analogous to previous studies in accordance with the Helsinki Declaration and after review by the responsible ethics committee of the University of Duisburg-Essen (19-9079-BO).[3,4]

The questionnaire with 124 questions was distributed to athletes aged 18 and older and filled in straightaway under

Figure 1
Showing an attack to score a goal during an underwater rugby (UWR) game



the supervision of medical staff who were available to answer questions and explain ambiguities.

Demographic data and information about injuries in ten different body regions (head, trunk, shoulder, elbow, wrist, finger, pelvis/thigh, knee, lower leg/ankle/foot, lungs) were collected. Participants were requested to answer yes/no questions about specific injuries and state the number of injuries sustained. The questionnaire could be answered in German or English. Most of the data was collected during two large competition events, the 10th European UWR Championship (26 June to 01 July 2017 in Helsinki, Finland) and the final of the 16th International Champions Cup (24–26 November 2017 in Berlin). Furthermore, in 2018 some clubs in North Rhine-Westphalia (Germany) were visited during training periods. The exposure time was extrapolated retrospectively from the current weekly training hours over the entire duration of the players' careers. To reduce the recall bias, the downtimes (time out of the game due to injury) were recorded individually according to body region and as total downtime, and then calculated as the average of the two downtimes. Bruises and superficial skin injuries were classified as "*minor*" injuries and distinguished from "*relevant*" injuries.

STATISTICAL ANALYSIS

The statistical evaluation was carried out using IBM SPSS Statistics 25 software (IBM, Armonk, NY, USA). Descriptive statistics included a calculation of means and standard deviations or medians and interquartile ranges where appropriate. All values were tested for normal distribution, with the Kolmogorov-Smirnov test and the Shapiro-Wilk test. The two-sided *t*-test was used for normally distributed values. For non-normally distributed values, the non-parametric Mann-Whitney U test was used to detect differences between unconnected test groups. Values of $P < 0.05$ were considered significant and $P < 0.001$ as highly significant.

Results

PARTICIPANTS

The study included 198 UWR athletes, 106 male (53.5%) and 92 female (46.5%). Within this group, 88.9% played in the Bundesliga or comparable leagues and 73.2% played internationally, while 6.5% played neither internationally nor in the Bundesliga (or comparable leagues). The

Table 1
Characteristics of male and female UWR players; **highly significant differences ($P < 0.001$); BMI – body mass index

Parameter	Males Median (IQR)	Females Median (IQR)
Age (years)**	33 (18)	28 (11)
Height (cm)**	180 (10)	169 (8)
Weight (kg)**	87.0 (18.5)	64 (12)
BMI ($kg \cdot m^{-2}$)**	26.6 (4.6)	22.5 (3.4)
Career duration (years)**	12 (15)	9 (13)
Exposure time (hours)	3,240 (3,780)	2,160 (4,428)
Training scope ($minute \cdot week^{-1}$)	300 (195)	360 (214)

Table 3
Types of injuries reported by the 198 underwater rugby players surveyed. Median injuries per player. As per Table 2, a relatively small number of players experienced large numbers of injuries. IQR – interquartile range

Injury	*n* (%)	Median (IQR)
Bruises	4,946 (52.2)	4.5 (14.0)
Sprains	3,353 (35.4)	4 (13.0)
Ligament ruptures	450 (4.8)	2.3 (7.8)
Fractures	161 (1.7)	0 (1.0)
Dislocations	136 (1.4)	0.7 (4.2)
Overload damage	431 (4.5)	2.2 (7.6)

characteristics of male and female UWR players are shown in Table 1.

INFLUENCE OF SEX ON INJURIES IN UWR

Male UWR players did not show significantly higher values in exposure time compared to female players ($P = 0.207$), but there were highly significant differences in age ($P = 0.001$), height ($P < 0.001$), weight ($P < 0.001$), BMI ($P < 0.001$) and career duration ($P = 0.005$) (Table 1).

The males, with median a total injury break 'downtime' of 4.8 (IQR 10.5) days, had to take longer breaks due to injuries than the female athletes with a median of 4.0 (8.6) days. Male players stated that they had a median of 18.5 (63) total injuries while playing UWR. Female players had a median of 20 (26.8) injuries.

INJURY MECHANISM

The most frequent cause of injury was '*player contact*' (81.8% of injuries), followed by '*injury from an attack*' (42.7%), '*injury from defense against the ball*' (33.9%), '*contact with equipment in general*' (22.9%), '*contact with fins*' (14.6%), '*contact with the ball*' (8.9%), '*out of the water*' (2.6%) and '*injuries caused by warming up*' (1.1%). The most severe injuries were also due to '*player contact*' (71.1%). Note, and injury can have more than one cause, hence these percentages sum to greater than 100%.

Table 2
Injury frequency according to anatomic location; Median injuries per player. A relatively small number of players experienced large numbers of injuries. IQR – interquartile range

Anatomic location	*n* (%)	Median (IQR)
Head injuries	8,082 (45.7)	4 (16)
Trunk	2,449 (13.8)	2 (7)
Shoulder	823 (4.6)	0 (3)
Elbow	1,018 (5.7)	1 (4)
Wrist	524 (3.0)	0 (2)
Finger	3,508 (19.8)	5 (11)
Pelvis and thigh	65 (0.4)	0 (0)
Knee	594 (3.4)	0 (2)
Lower leg/ankle/foot	565 (3.2)	0 (1)
Pulmonary diseases	12 (0.1)	0 (0)
Blackout	61 (0.3)	0 (0)
Total injuries	17,701 (100)	

Table 4
Locations of the 161 fractures reported by the 198 underwater rugby players surveyed

Fracture location	*n* (%)
Finger	47 (29.2)
Ribs	22 (13.7)
Ankle	22 (13.7)
Carpal bones	21 (13.0)
Nose	16 (9.9)
Wrist	12 (7.5)
Elbow	7 (4.4)
Lower leg	6 (3.7)
Mandible	4 (2.5)
Foot	4 (2.5)

INJURY FREQUENCY

A total of 17,701 injuries occurred in 755,569 training hours. Each player suffered a median of 19.5 (IQR 44) injuries. Based on the exposure time, means of 37.7 (SD 90) injuries per 1,000 playing hours per player and 9.9 (20.1) injuries per year were found. Three percent of the respondents ($n = 6$) stated that they had never suffered an injury during UWR. The exact distribution of injuries according to body region is shown in Table 2.

TYPE OF INJURY

The most common types of injury were bruises (52.2%) and sprains (35.4%). Table 3 shows the most common types of

Table 5
Head and finger injuries reported as mean (SD) injuries per player among the 198 players surveyed

Injury type	Mean (SD)
Head injuries	
Abrasions	18.5 (118.3)
Nosebleeds	10.5 (75)
Lacerations	4.4 (37.7)
Lip bites	1.5 (3.6)
Tongue bites	1.4 (5.3)
Concussions	0.4 (1.6)
Eardrum injuries	0.2 (0.6)
Tooth loss	0.2 (0.6)
Nose fractures	0.1 (0.3)
Mandibular fractures	0.02 (0.2)
Cerebral haemorrhage	0.02 (0.1)
Finger injuries	
Finger contusions	13 (48.3)
Finger compressions	4.3 (13.3)
Tendon injuries	1.5 (7.6)
Finger dislocations	0.5 (4.3)
Finger fractures	0.2 (1.5)

injuries. A total of 161 fractures occurred, which are shown in Table 4. Notable injuries were mainly found in the head region followed by finger injuries, which are shown in Table 5. The distribution of fractures of the fingers was as follows: Thumb (digit I) = 14.28%, digit II = 0%, digit III = 28.6%, digit IV = 14.3% and digit V = 42.9%.

INFLUENCE OF BMI

Regarding physical characteristics, 106 (54.5%) players were of normal weight, 66 (33.8%) were overweight, 19 (9.7%) had grade 1 obesity, three (1.5%) had grade 2 obesity and one (0.5%) had a grade 3 obesity according to the BMI classification of the World Health Organisation.[5] Three players did not provide any weight information. The normal weight players had to pause for a median of 4 (IQR 7.8) days due to injuries whereas overweight players had a median of 5 (9) days injury downtime. Among the obese players, the total number of injuries suffered by the individual players decreased the higher their BMI was.

Discussion

To the best of our knowledge, this is the first study to record UWR injuries in a large international player collective. One hundred and ninety-eight active UWR players participated in the study which enabled compilation of a comprehensive overview of this so far insufficiently investigated sport. The limitations of the study are the retrospective design and the inherent recall bias of such investigations. Data such as weight, size, game class, game equipment and training frequency only represent snapshots, so that we did not investigate correlations between game class and injuries. Since only active players were interviewed, serious injuries that resulted in players retiring from the sport may not be adequately recorded. The injury incidences determined are known to depend on the study design and tend to be underestimated in retrospective examinations.[6] It was decided to record all injuries in order to be able to map the sports medicine relevance of UWR more precisely.

INJURY MECHANISM, TYPES AND FREQUENCY

The most frequent injuries in UWR occur through player contact (81.8%) followed by injuries from an attack by an opponent (42.7%). Similar data have been reported in rugby. Here, the most common cause of injury is an opponent's tackle,[7] being responsible for 40% and 48% injuries in two studies.[8,9] Others reported that 80% of all injuries in rugby sport happen during a contact event.[10] These numbers are similar to those in UWR. Water polo is very similar to UWR. It is a team sport which combines swimming sprints and eggbeater kicking, frequent overhead movements and throwing, and regular physical contact. In water polo, player contact is mentioned as one of the most common causes of injury. During the 2004 Olympic Games in Athens, Greece, 56% of the reported injuries in water polo were incurred by contact with another player.[11] The present study also showed that the most common injuries in UWR are caused by player contact, however, foul play was not mentioned as significant. In water polo, most fouls take place underwater, which is difficult for the referee to recognise.[12] In UWR there are three referees who can only concentrate on the underwater scenes. The excessive amount of leg work results in degenerative lower extremity injuries in water polo, which we did not find in UWR. Despite the influence of body contact in water polo, the ball was found to be the second most important risk factor. A third of injuries (33.9%) were caused by defending the ball and 8.9% by contact with the ball.[13,14] Unlike in UWR, which is played underwater without throwing movements, the repeated overhead throwing by water polo players introduces an increased risk for injuries and problems in the shoulder.[15] In the present study, 22.9% of injuries were due to "*contact with equipment in general*" and 14.6% to "*contact with fins*". Other protective equipment, e.g., mouthguards, is not used in UWR, as these would most likely be a hindrance underwater.

The frequency of injuries in water polo is higher than in UWR. There were 37.7 (SD 90) injuries per 1,000 playing hours in the present study compared with 56.2 (6.7) injuries per 1,000 playing hours in water polo.[16] This may be due to the fact that in the study in water polo players took place mainly under competition conditions.[16]

The most significant injuries in UWR were found in the regions of the head and fingers. The most common water polo injuries were laceration (12.7%) and contusion (10.9%) of the head, followed by (sub-) luxation/sprain of the hand (9.5%) and contusion of the trunk (6.5%) or hand (6.2 %).[16] These results correspond to those that we recorded for UWR. We did not find any accumulation of hamate fractures in

UWR, as described in a prior case series in UWR.[17] The majority of water polo injuries observed during the last three FINA World Championships occurred during competition with 10% to 23% of surveyed athletes reporting injuries.[18] This has not yet been sufficiently investigated for UWR. One study highlighted a higher risk of finger injuries in American football and rugby than in other sports. Contact with the ball was given as the reason.[19] Differences with other injury prone sports is probably related to the fact that UWR is played underwater and although it is a hard contact sport, the impact of contacts/tackles and movements is absorbed and lessened by the water.

In the present study, 2,290 weeks of break time from play were lost due to injuries in UWR. This is an average total break time per player of 11.6 weeks. This is a longer injury duration than is reported for example in rugby at 7.6 weeks per player.[20] Our study showed a total of 17,701 injuries in 755,569 training hours. The UWR players interviewed had suffered a median 19.5 (IQR 44) injuries. This is a high number and underlines how physical and risky UWR is for the player. In terrestrial rugby, the frequency of injuries is lower. When normalised to exposure time, the present UWR study showed an average of 37.7 (SD 90) injuries per 1,000 hours of play or 9.9 (20.1) injuries per player per year. In a study of 803 amateur and professional rugby players who completed an average of 21.9 matches per player the injury frequency was 16.4 (14.8 to 18.1) per 1,000 playing hours.[9]

INFLUENCE OF SEX AND BMI ON INJURIES

The female UWR players in our survey sustained more injuries than male UWR players. One explanation could be that male UWR players have more strength and are probably more athletic than female players. On the other hand, male players had to take longer breaks due to injuries than the female players in our study. One reason for this could be a higher injury severity in male players. Further possible reasons should be established in follow-up studies. Current studies of other sports also show gender-specific differences with regard to injuries. The National Collegiate Athletic Association (NCAA) recorded all injuries for men's and women's swimming and diving teams over five years. Interestingly, female swimmers had a 58% higher rate of overuse injuries compared with male swimmers.[21] In contrast to UWR, most injuries were caused by overwork and did not affect the head but the shoulder.[22] However, it depends on the sport itself whether female or male athletes are affected more often, and which body region is injured more often.[23,24]

Over half of all the UWR players surveyed were of normal weight (54.5%). In this study, the number of days off due to injury increased with the rise in BMI. Obese UWR players showed the highest number of total injuries. This group was followed by the normal-weight players. In the group of obese UWR players, the total number of injuries sustained by individual players decreased the higher the BMI was. In contrast to these results, other studies on various sports have observed a correlation between susceptibility to injury and increasing BMI.[25,26] The results of this study could be explained by the underwater playing environment. The actions of UWR players with a higher BMI are supposedly slower, so that less force arises in collisions.

Conclusions

This is the first epidemiological survey of injuries in UWR that the authors are aware of. The analysis shows a predominance of injuries in the head region followed by injuries to the fingers and minor musculoskeletal injuries. Despite sometimes fierce physical contact, the risk of injury is low compared to some other ball sports. Injuries to the lower extremities are particularly infrequent. The reasons for this are, on the one hand, the three-dimensional playing field and the cushioning effect of the water and on the other, the strict rules of the game and the intensive referee policing of these rules. In summary, the injury mechanism and the type of injury in UWR are comparable to other similar sports, such as rugby football, water polo or other water sports. It will be interesting in following studies to record chronic injuries in UWR. Further studies are necessary to produce an overall assessment of this sport and establish measures to prevent injury.

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Perioperative hyperbaric oxygen treatment and postoperative complications following secondary breast reconstruction after radiotherapy: a case-control study of 45 patients

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Key words
Cancer; Hyperbaric research; Outcome; Soft tissue radionecrosis; Surgery; Women

Abstract
(Meier EL, Hummelink S, Lansdorp N, Boonstra O, Ulrich DJO. Perioperative hyperbaric oxygen treatment and postoperative complications following secondary breast reconstruction after radiotherapy: a case-control study of 45 patients. Diving and Hyperbaric Medicine. 2021 September 30;51(3):288–294. doi: 10.28920/dhm51.3.288-294. PMID: 34547780.)
Introduction: Radiotherapy reduces the risk of locoregional recurrence of breast cancer. As a side-effect, tissue can become hypocellular, hypovascular, and hypoxic and late radiation tissue injury can develop months or years later. Radiotherapy increases the risk of complications following secondary breast reconstruction. Hyperbaric oxygen treatment (HBOT) improves oxygenation of irradiated tissue and induces neovascularisation. This study evaluated whether the incidence of complications following secondary breast reconstruction after radiotherapy is decreased with perioperative HBOT.
Methods: In this retrospective case-control chart review study, patients who underwent perioperative HBOT (n = 15) were compared to lifestyle-matched (n = 15) and radiation damage-matched (n = 15) patients who underwent secondary breast reconstruction without HBOT.
Results: The HBOT group had significantly more severe radiation damage of the breast than the lifestyle- and radiation-damage-matched control groups (scoring grade 1–4, mean 3.55 versus 1.75 and 2.89 respectively, P = 0.001). Patients underwent on average 33 sessions of HBOT (18 sessions preoperatively and 15 sessions postoperatively). There was no significant difference in the incidence of postoperative complications between the HBOT group, lifestyle-matched group and radiation damage-matched group. Logistic regression analysis showed a lower risk of postoperative complications in patients who underwent HBOT.
Conclusions: Although the HBOT group had more radiation damage than the control groups, the incidence of postoperative complications was not significantly different. This implied a beneficial effect of HBOT, which was supported by the logistic regression analysis. Definitive conclusions cannot be drawn due to the small sample size. Future research is justified, preferably a large randomised controlled trial.

Introduction

Breast reconstruction following breast-conserving therapy or mastectomy is a common procedure in women with breast cancer. If radiotherapy is indicated as part of their cancer treatment, the breast reconstruction will be delayed in most patients, and thus, secondary breast reconstruction will be performed. Radiotherapy reduces the risk of locoregional recurrence of the disease, leading to an increased overall survival rate, both after breast-conserving treatment and mastectomy.[1] The average radiotherapy dose is 50 Gray.[2] Although radiotherapy improves overall survival, it has various side-effects. Radiotherapy causes cellular depletion, microvascular impairment, fibroblast dysfunction, extracellular matrix alterations and growth factor derangement.[3] This results in hypocellular, hypovascular and hypoxic tissue.[4]

Acute side-effects of radiotherapy, that occur within days or weeks, are dose- and time-dependent and include erythema, inflammation, oedema from leaking capillaries and desquamation. Delayed effects of radiotherapy occur months or even years later and are known as late radiation tissue injury (LRTI). LRTI consists of soft tissue fibrosis, skin atrophy, epithelial ulceration, skin necrosis, major vessel rupture and impaired wound healing.[5,6] LRTI decreases the ability of the tissue to heal following a breast reconstruction, which predisposes to postoperative complications.

Breast reconstructions in the irradiated breast have higher complication rates and poorer aesthetic outcomes compared to reconstructions in non-irradiated breasts (relative risk of 2.58 [95% CI 1.86–3.57]).[7,8] Autologous reconstructions are preferred over reconstructions with implants since the

latter have a high incidence of capsular contracture (up to 40–50%).[9–13]

However, in autologous reconstructions, vascular changes of the recipient site increase the risk of perioperative vascular complications such as arterial or venous thrombosis and the need to re-perform the anastomosis.[14] Other radiotherapy-related complications in autologous reconstructions include fat necrosis, fibrosis, atrophy and flap contracture.[15–17] Therefore, breast reconstructions in irradiated tissue remain challenging.

Hyperbaric oxygen treatment (HBOT) consists of breathing 100% oxygen in a hyperbaric chamber at a pressure of 202.6–253.3 kPa (2.0–2.5 atmospheres absolute). Each treatment session has a duration of about 2 hours. The treatments are given five days per week for a total of 30–40 sessions (6–8 weeks, excluding weekends). HBOT improves oxygenation of the hypoxic radiated tissue, resulting in oedema reduction, phagocytosis activation, anti-inflammation, neovascularisation, osteogenesis and stimulation of collagen formation by fibroblasts.[18] These processes could be of value to reduce complications following secondary breast reconstruction in the previously irradiated breast. Previous studies have shown that LRTI symptoms of the breast improve following HBOT.[19–21] Reduction of pain and hypersensitivity of the affected breast and fewer skin problems in the affected area are reported, as well as a reduction of pain and swelling in the affected shoulder, arm and hand.[21] Apart from LRTI of the breast, HBOT is used for several other indications, such as the treatment of necrotizing soft-tissue infections, osteomyelitis, acute thermal burn injury, crush injury, chronic ulcer due to diabetes, compromised grafts and flaps, radiation cystitis, proctitis and enteritis and other late radiation tissue injury.[18,22]

Several case reports and a rat model study describe the beneficial effect of HBOT on skin flap ischaemia after mastectomy, skin flap necrosis after mastectomy with direct reconstruction with implants, and skin survival after a transverse rectus abdominus myocutaneous (TRAM) flap.[23–30]

Based on this literature, HBOT could have a beneficial effect on postoperative complications of secondary breast reconstruction. However, evidence about the use of HBOT specifically in secondary breast reconstruction is limited to one case-control study with five patients (10 breasts).[31] Therefore, the aim of this study was to investigate whether the incidence of complications following secondary breast reconstruction decreased with perioperative HBOT.

Methods

A retrospective cohort study was conducted, using the STROBE statement guidelines.[32] Approval of the medical ethical committee was obtained (file number 2018-4394). Written informed consent was obtained from all subjects.

PATIENT SELECTION

All patients referred by the Department of Plastic Surgery in the Radboudumc (Nijmegen, the Netherlands) to the Da Vinci Clinic (Arnhem, the Netherlands) to undergo perioperative HBOT for secondary breast reconstruction after radiotherapy were included. All of these patients underwent radiotherapy because of breast cancer and substantial radiation damage was seen upon referral for the secondary breast reconstruction.

To add a control group to the study, the main factors influencing the outcome of breast reconstruction were determined based on literature and expert opinion.[33,34] Demographic factors and radiation damage developed after radiation were determined as principal factors influencing the outcome of breast reconstruction. To take both factors into account, two control groups were created. Patients with a history of secondary breast reconstruction following radiotherapy because of breast cancer were extracted from a Radboudumc database. Exclusion criteria were no radiotherapy, perioperative HBOT, patients who already underwent HBOT in the past, patients with certain co-morbidities (history of thoracic surgery, history of a major vascular event, immunosuppressive treatment, or pre-existent coagulation disorders) and patients who were deceased at the time of the study.

The first control group was case-matched with the HBOT group based on year of birth, body mass index (BMI), co-morbidities (hypertension, diabetes mellitus, a history of deep vein thrombosis (DVT), pulmonary embolism or thrombosis elsewhere, use of platelet aggregation inhibitors, use of anticoagulants) and smoking status. For each of the patients of the HBOT group, the best match was chosen and included.

The second control group was matched based on radiation damage. For every woman in the HBOT group, the radiation damage was classified by the reviewer (EM) using the toxicity scoring system of the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer.[35] Again, the best match based on this score was chosen and included in the second control group.

OUTCOMES AND ASSESSMENT

The electronic medical records of the Radboudumc of all patients were retrospectively reviewed by one independent reviewer (EM). For the HBOT group, the medical records of the Da Vinci Clinic were also reviewed by the same reviewer. Outcomes and relevant data as described were recorded in an online database (Castor EDC, Amsterdam, the Netherlands).[36]

The primary outcome of this study was the number of postoperative complications of the breast, as described in postoperative clinical notes. Postoperative complications

were defined as the need for reoperation, postoperative bleeding, infection, flap loss and wound healing problems with necrosis. A complication was registered if any of the terms above were mentioned in the clinical notes. Postoperative bleeding was registered as a complication if bleeding occurred which required surgery to stop the bleeding. Infection was registered as a complication if the term infection was mentioned, or if infection symptoms (erythema, swelling, increase of temperature, pus discharge) were described with the prescription of antibiotics. Necrosis was registered as a complication if a necrosectomy was performed.

Other perioperative outcomes such as type of reconstruction, duration of surgery and duration of ischaemia of the deep inferior epigastric artery perforator (DIEP) flap and postoperative recovery days in the hospital were also recorded.

Other relevant data recorded included patient demographics, risk factors, and disease characteristics including radiation damage and treatment characteristics. The following risk factors were noted; hypertension, diabetes mellitus, a history of deep vein thrombosis (DVT), pulmonary embolism or thrombosis elsewhere; use of platelet aggregation inhibitors, use of anticoagulants, smoking history, and obesity (body mass index [BMI] ≥ 25.0). The amount of radiation damage was classified using the scoring system as previously mentioned.[35] To classify each patient, clinical notes of physical examination, as well as preoperative photographs, were reviewed to estimate the grade of radiation damage.

Follow up assessments of patients were very different. Therefore, outcome measures were scored up to 6 months postoperative. All patients had at least two follow up assessments in this period.

In the HBOT group, the number of sessions of HBOT and side effects were also recorded.

STATISTICAL ANALYSIS

SPSS version 25 (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, V.A., NY: IBM Corp.) was used for statistical analysis. A Kruskal-Wallis one-way analysis of variance was performed per patient to compare the medians of the three groups. The Kruskal-Wallis analysis was performed on patient characteristics, perioperative outcomes, postoperative complications, time of ischaemia (when applicable), bilateral reconstruction, surgery time and length of hospital stay, and was analysed for each type of reconstruction separately. Bonferroni correction was performed to correct for multiple testing.

A multivariate logistic regression analysis was performed to test the research hypothesis regarding the relationship between the likelihood of postoperative complications based on treatment with or without HBOT and the amount of radiation damage. The presence or absence of postoperative complications was the dependent variable. Treatment with or without HBOT and amount of radiation damage were independent variables.

The following equation was used:
$\log[Y/1\text{-}Y] = \beta_0 + \beta_1 * \text{HBOT} + \beta_2 * \text{radiation damage}$.

Y = postoperative complications, coded as 0 = no postoperative complications and 1 = postoperative complications, HBOT is coded as 0 = no HBOT and 1 = HBOT, and radiation damage is coded following the earlier mentioned toxicity score, ranging from 0 = no radiation damage to 4 = grade 4 radiation damage. Thus, the predicted logit of postoperative complications was found to be: $-2.282 - 0.362 * \text{HBOT} + 0.254 * \text{radiation damage}$.

In all statistics, a *P*-value of ≤ 0.05 was considered as significant.

Results

In total, the patient population consisted of 45 women. In the HBOT group, five patients were excluded due to incomplete data sets. A remaining total of 15 eligible patients where a full data set was available were included. In the control groups, 30 patients were included, 15 in each group. Patients in the HBOT group had undergone HBOT and reconstructive surgery in the period between 2013 and 2017. Patients in the control groups had undergone reconstruction surgery in the period between 2016 and 2018.

PATIENT CHARACTERISTICS

Patient characteristics are presented in Table 1. Reconstructions performed in the groups were: DIEP reconstruction, both unilateral and bilateral; latissimus dorsi (LD) reconstructions, both with and without implants; and one reconstruction with implants following tissue expanders.

There were no significant differences between the demographics of patients. Despite an attempt to match the HBOT group with one of the control groups, there was a significant difference between the groups in the amount of radiation damage, the HBOT group had the most radiation damage (mean radiation damage score 3.55 in the HBOT group versus 1.75 in the lifestyle-matched group and 2.89 in the radiation-damage-matched group, $P < 0.001$). Median scores are presented in Table 1.

HBOT SESSIONS

On average, 33 sessions of HBOT were given to patients (mean of 18.4 preoperatively and 14.7 postoperatively, range of 14–50 sessions). There was no correlation between number of sessions and radiation damage. Three patients failed to complete the prescribed number of sessions. Reasons for not finishing the complete treatment (treatment

Table 1
Baseline patient characteristics. All three groups *n* = 15. DIEP – deep inferior epigastric artery perforator flap; IQR – interquartile range

Patient characteristics	Lifestyle-matched group Median (IQR) or *n* (%)	Radiation damage-matched group Median (IQR) or *n* (%)	HBOT group Median (IQR) or *n* (%)	*P*-value
Age at surgery	54 (47–61)	58 (50–64)	55 (47–61)	0.547
Body mass index	27 (26–30)	26 (24–29)	26 (24–28)	0.642
Never smoked	7 (47%)	10 (67%)	7 (47%)	0.456
Risk factors	1 (1–2)	2 (1–2)	1 (0–2)	0.215
Radiation damage Grade 0 Grade 1 Grade 2 Grade 3 Grade 4	1 (1–2) 1 (13%) 4 (27%) 2 (13%) 1 (7%) 1 (7%)	3 (2–3) 0 (0%) 0 (0%) 4 (27%) 7 (47%) 3 (20%)	4 (3–4) 0 (0%) 0 (0%) 0 (0%) 7 (47%) 6 (40%)	< 0.001
Chemotherapy	13 (87%)	12 (80%)	14 (93%)	0.862
Hormone therapy	7 (47%)	5 (33%)	5 (33%)	0.691
Axillary lymph node dissection	9 (60%)	4 (27%)	7 (47%)	0.314
DIEP unilateral	10 (67%)	7 (47%)	5 (33%)	0.192
DIEP bilateral	5 (33%)	3 (20%)	4 (27%)	0.717
Latissimus dorsi	0 (0%)	5 (33%)	5 (33%)	0.430
Tissue expanders	0 (0%)	0 (0%)	1 (7%)	0.368

Table 2
Postoperative complications. Note that percentage calculations are on a small denominator (*n* = 15 all groups)

Postoperative event	Lifestyle-matched group *n* = 15 *n* (%)	Radiation-damage-matched group *n* = 15 *n* (%)	HBOT group *n* = 15 *n* (%)	*P*-value
No complications	12 (80)	13 (87)	12 (80)	0.925
Repeat surgery	2 (13)	1 (7)	2 (13)	0.797
Postoperative bleeding	0 (0)	0 (0)	1 (7)	0.387
Infection	2 (13)	1 (7)	2 (13)	0.797
Necrosis	1 (7)	0 (0)	1 (7)	0.387
Flap loss	1 (7)	0 (0)	1 (7)	0.633

as prescribed at intake, range 30–40 prescribed sessions) were severe flu, not feeling well and surgery performed earlier than planned. During HBOT, two patients suffered from trouble equalising middle ear pressure, three from myopia, and five from tiredness. All of these side effects were reversed after the treatment.

PRIMARY OUTCOME: POSTOPERATIVE COMPLICATIONS

Complications are presented in Table 2. Overall, there were no significant differences in the occurrence of postoperative complications between groups. Reasons for repeat surgery were necrosis, suspicion of venous congestion, arterial problems or postoperative bleeding. All complications occurred within the first three postoperative months.

According to the multivariate logistic regression model, the logit of a patient having postoperative complications was positively related to radiation damage (0.254) and negatively related to HBOT (-0.362), as can be seen in Table 3. In other words, the higher the radiation damage, the more likely it is that a patient would have postoperative complications. And given the same radiation damage score, patients receiving HBOT were less likely to have postoperative complications. However, with *P*-values of 0.528 and 0.684 respectively, these results were not significant.

PERIOPERATIVE PARAMETERS

Time of surgery of all reconstructions, time of ischaemia of the unilateral and bilateral DIEP and amount of recovery days in the hospital were all not significantly different between the three groups. Perioperative parameters are presented in Table 4.

Table 3

Logistic Regression Analysis of the relationship between the likelihood of postoperative complications based on treatment with or without HBOT and the amount of radiation damage. [a] – variables entered on step 1 were HBOT, radiation damage; Beta – coefficient for the constant (intercept); CI = confidence interval; df – degrees of freedom for the Wald Chi-Square test; Exp (β) – exponentiation of the β coefficient (odds ratio); SE – standard error; Wald – Wald Chi-Square that tests the null hypothesis that the constant equals 0

Variables in the equation		Beta	SE	Wald	df	*P*	Exp (beta)	95% CI for Exp (beta)	
								Lower	Upper
Step 1[a]	HBOT	-0.362	0.890	0.165	1	0.684	0.697	0.122	3.984
	Radiation damage	0.254	0.403	0.399	1	0.528	1.290	0.586	2.839
	$Beta_0$	-2.282	1.096	4.330	1	0.037	0.102		

Table 4

Relevant perioperative parameters including total surgery time for the DIEP and LD flap reconstructions, time of ischaemia of DIEP reconstructions, and total recovery days in the hospital for all reconstructions. DIEP – deep inferior epigastric artery perforator reconstruction; LD – latissimus Dorsi reconstruction

Parameter	Lifestyle-matched group Mean (SD)	Radiation damage-matched group Mean (SD)	HBOT group Mean (SD)	*P*-value
DIEP unilateral (hours)	7.3 (1.3)	7.2 (1.3)	7.0 (1.5)	0.673
DIEP bilateral (hours)	9.5 (0.7)	11.1 (3.6)	9.3 (3.3)	0.651
LD (hours)	-	2.7 (0.8)	3.8 (2.0)	0.299
Time of ischaemia DIEP unilateral (minutes)	72.0 (24.9)	57.0 (20.1)	61.0 (25.9)	0.485
Time of ischaemia DIEP bilateral (minutes)	69.0 (18.2)	36.0 (14.0)	59.0 (7.4)	0.350
Total hospital days	5.8 (1.2)	5.1 (1.2)	5.6 (3.1)	0.581

Discussion

Radiotherapy plays an essential role in the treatment of women with breast cancer by increasing the overall survival rate.[1] However, radiotherapy can lead to hypocellular, hypovascular, hypoxic tissue and LRTI, which decreases the ability of the tissue to heal.[4]

As a consequence, breast reconstructions in the irradiated breast have higher complication rates compared to reconstructions in the non-irradiated breast (relative risk of 2.58, 95% CI 1.86–3.57).[8] HBOT can decrease the effects of LRTI by improving oxygenation of the damaged tissue, resulting in neovascularization, anti-inflammation and stimulation of collagen formation by fibroblasts.[19] This is one of the first studies examining the effect of HBOT on perioperative outcomes and postoperative complications of secondary breast reconstruction after radiotherapy.

Using logistic regression analysis, a beneficial effect of HBOT was demonstrated on postoperative complications of breast reconstruction after radiotherapy, although this effect was not significant. However, there was a significant difference in the amount of radiation damage, with a higher score in the HBOT group ($P < 0.001$). Although the aim was to form a control group as similar as possible, it was not possible to find an equal number of patients with grade 4 radiation damage as in the HBOT group.

The finding that, despite the HBOT group having significantly more radiation damage, the postoperative complications and perioperative outcomes in all groups were not significantly different, supports the conclusion that HBOT provided a beneficial effect. HBOT was well tolerated with no major side effects occurring. The average number of sessions of HBOT was 33, which is similar to the average number of sessions that have been given in other studies for other chronic indications, including LRTI.[37,38]

In the literature, there is evidence for a beneficial effect of HBOT on wound healing processes,[22] however, there is little evidence for the effect of HBOT on postoperative outcomes. A randomised controlled trial examining the influence of HBOT on split-thickness skin grafting showed an increased survival of skin graft surface area of 29% with the use of HBOT. Complete take of the skin graft was 64% in the HBOT group versus 17% in the control group.[39] Another study reported a significantly lower postoperative infection rate in neuromuscular surgery, with 5.5% infections in the HBOT group versus 16.6% infections in the non-HBOT group.[40]

A major limitation of this study was the significant difference in the amount of radiation damage between patients. Although all other patient characteristics (age at surgery, BMI, smoking history, risk factors) and neoadjuvant therapy (chemotherapy, hormone therapy, axillary lymph node

dissection) were not significantly different, the significant difference in the amount of radiation damage created selection bias.

Another limitation of this study was its retrospective design. Not all notes were recorded in a standardised fashion. Therefore, the grade of radiation damage had to be estimated based on clinical notes and preoperative photographs. The interpretation of minor versus major complications was in some cases challenging. To retain objectivity, complications were only registered if there was a clear outcome measure, for example, a necrosectomy in case of necrosis. However, this method can possibly lead to bias. The study was also small.

This study provides evidence that HBOT may reduce postoperative complications in women undergoing secondary breast reconstruction in the irradiated breast. Embedding HBOT as a method of work-up treatment in cases of heavily irradiated secondary reconstruction may be considered. More research is needed in a larger patient group to evaluate the effect of HBOT on perioperative and postoperative outcomes. For a future study, a large randomised controlled trial would be preferable.

Conclusion

Although the group that underwent HBOT had more radiation damage than the control groups, the incidence of postoperative complications was not significantly different. This implied a beneficial effect of HBOT. However, explicit conclusions cannot be drawn due to the small sample size. Future research is justified, preferably a large randomised controlled clinical trial.

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Short communication

Proof-of-concept for a segmented composite diving suit offering depth-independent thermal protection

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Abstract

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Heat loss is a major health hazard for divers. It can lead to hypothermia, organ damage, unconsciousness, and eventually death. Hence, thermal protection is essential for diver safety. Typically, protection is provided by wetsuits made of bubbled neoprene. However, neoprene shrinks with depth and loses thermal insulation capability, while thick neoprene suits make swimming exhausting. Herein, a proof-of-concept is presented for a solution to both problems: a 'K-suit' made of thermally-resistive composite segments attached to a thin neoprene suit. The segments are made of hollow glass microspheres embedded in carrier polymer thermally cured in 3D-printed molds based on 3D-scans of the diver's body. The K-suit was compared in field trials with a 7 mm commercial neoprene suit by diving in pairs, while automated dataloggers registered pressure and temperature inside and outside both suits. The K-suit demonstrated +4ºC higher temperature difference than the 7 mm neoprene. Also, divers reported that the K-suit had the ergonomics of a 3 mm neoprene suit. These preliminary results represent a proof-of-concept for the K-suit and promise further improvements with potential impact on diver safety.

Introduction

Diving is a potentially dangerous undertaking for humans. Heat loss is one of its major hazards. Compared to air, sea water has ~24x greater thermal conductivity and ~4x greater specific heat capacity.[1] As a result, even well-adapted sea mammals lose heat to ambient water up to 4.5x faster than in air at the same temperature difference.[2] That heat loss[3] means hypothermia[4] occurs far more rapidly in submerged humans.[5] As the diver's core temperature declines, the diver runs the risk of organ damage, loss of consciousness and eventually death. It takes ~1 h in 10°C water or ~15 min in 5°C water for an unprotected lean human to reach hypothermia.[6] Even extensively trained and conditioned divers cannot compensate for the heat loss.[7] Hence thermal protection is critical, particularly in longer dives and in cold waters.

The typical thermal protection is a wetsuit comprised of neoprene (3–8 mm in thickness) encased between two thin layers of cloth (0.5–1 mm thick). During fabrication, the neoprene is 'bubbled' with air or nitrogen to form microscopic pockets, which provide the thermal insulation and mechanical flexibility to the suit. Protected by a neoprene wetsuit, a lean diver in 5°C water would reach hypothermia in ~1 h in a 3 mm suit and in ~1.5 h in a 5 mm suit.[6] Thicker suits offer more protection but are less flexible, constrain ranges of motion and fatigue the diver faster. Consequently, current suits do not exceed 8 mm in thickness. Furthermore, the air bubbles in the neoprene are easily compressible, so the insulation is reduced as depth and ambient pressure increase.[8] For example, neoprene loses ~50% of its thermal protection at 30 metres of seawater (msw).[9]

We developed a composite material made of hard hollow microspheres embedded in carrier polymer.[9] We experimentally showed that the composite offers more thermal protection than bubbled neoprene and also retains its thermal protection at depth.[9]

However, the composite is less flexible than neoprene, and so cannot be tailored like cloth. Instead, we built a segmented suit (the 'K-suit'), wherein monolithic plates of the composite material cover body areas that do not bend, while areas of significant bending are left to thin neoprene. In this proof-of-concept study, we briefly describe the design and fabrication process, and present preliminary results of field tests to show proof-of-concept.

Figure 1
Suit design and fabrication; the diver's 3D body scans (A) were ergonomically segmented (B) and converted into mold designs (C, D). The molds were 3D-printed in polycarbonate and used to cast composite segments (E). The segments were fitted (F, G) to the diver, trimmed, and sealed in external pockets on a 3 mm neoprene suit, to produce the K-suit (H)

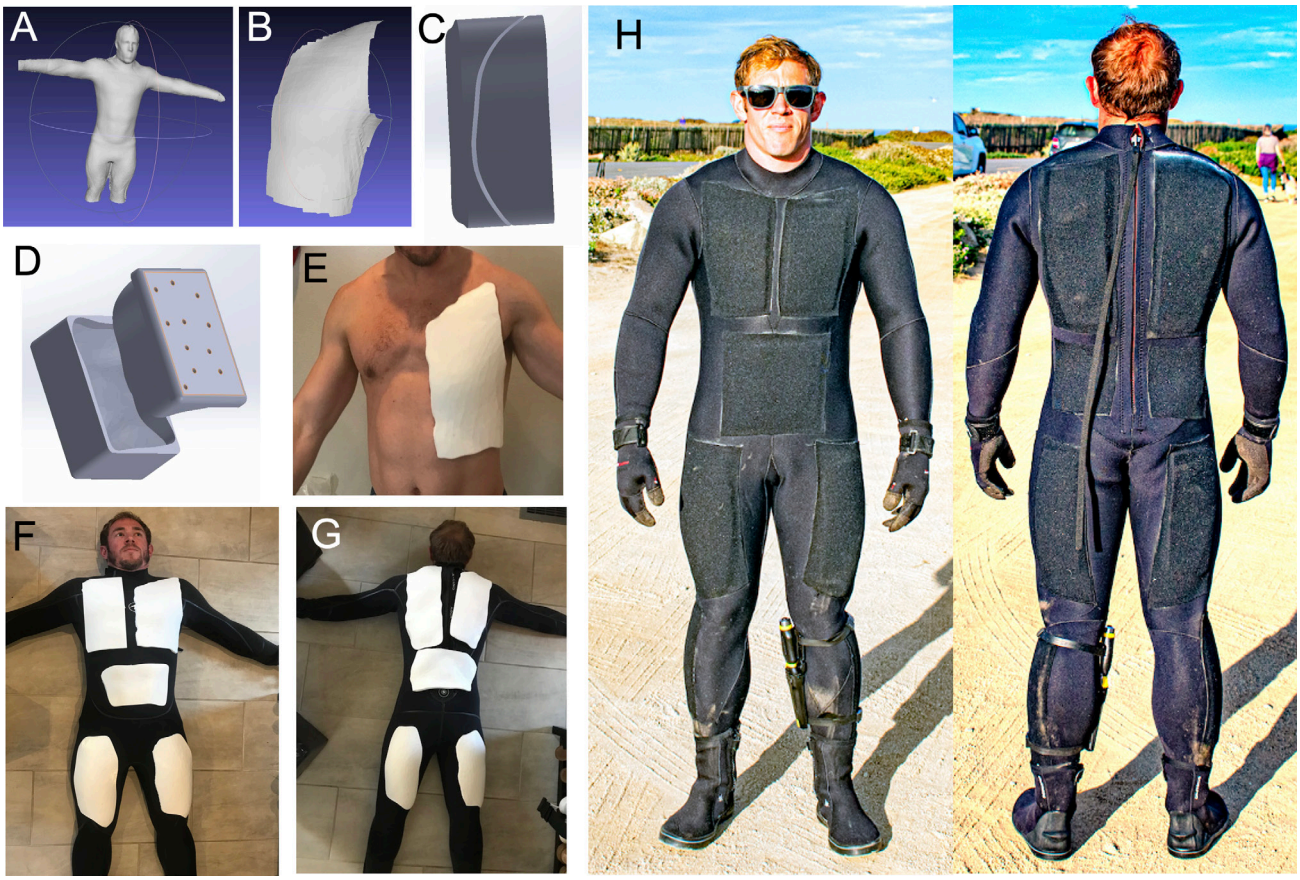


Table 1
Biometric data for the paired divers; BMI – body mass index

Divers	Age (years)	Height (m)	Weight (kg)	BMI kg·m^{-2}
K-suit	28	1.68	77	27.4
7mm neoprene	34	1.83	111	33.2

Methods

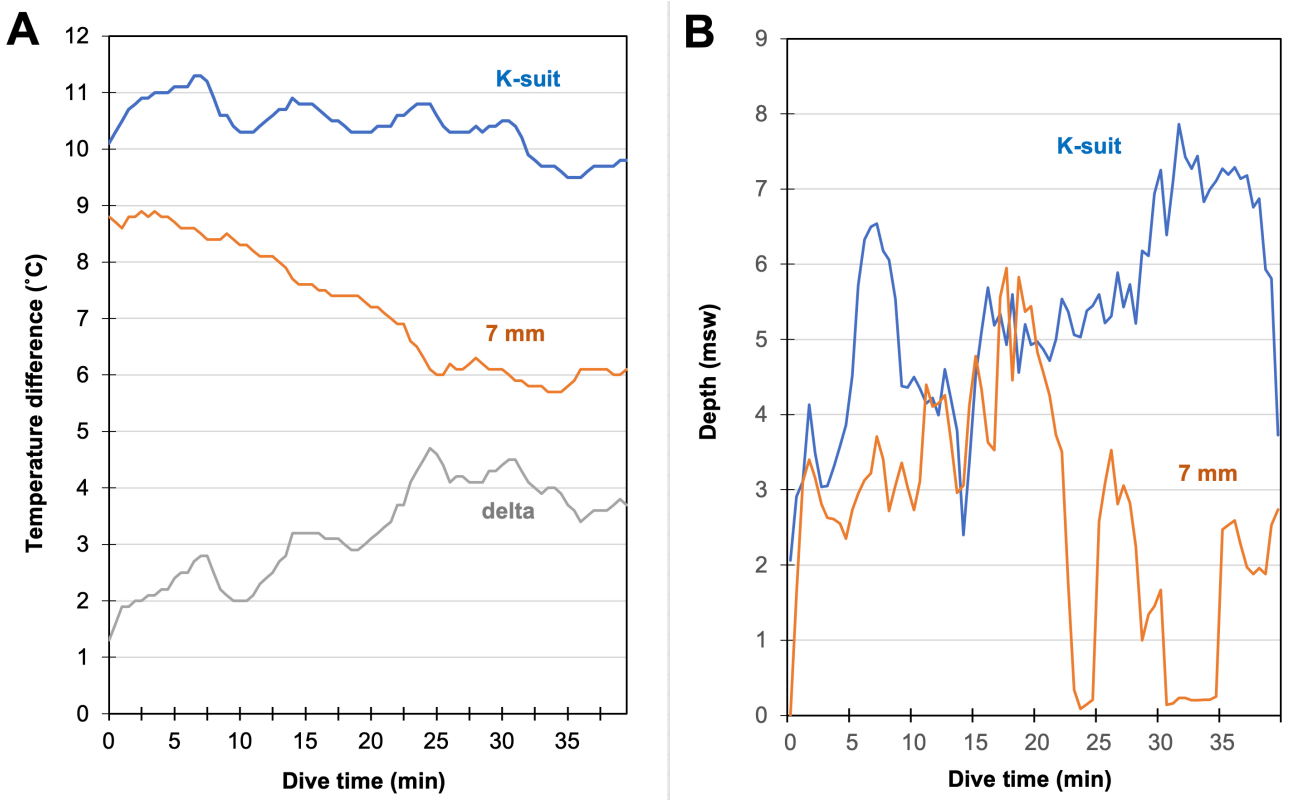
Field test plans were reviewed and approved by the Institutional Review Board (IRB) at the Naval Postgraduate School (NPS).

Three-dimensional (3D) body scans (Figure 1A) of divers wearing thin neoprene suits were generated by a portable scanner attached to an iPad. The scans were smoothed, simplified, converted to stereolithography (STL) format in MeshLab (Figure 1B) and converted into 3D mold designs in SolidWorks (Figure 1C, D). The designs were 3D-printed in polycarbonate at half-density mesh on a Fortus 400mc 3D printer (Stratasys, Eden Prairie, MN, USA). Sylgard 184 (Dow Corning, Midland, MI, USA) prepolymer was mixed with K1 hollow glass microspheres (3M, Saint Paul, MN, USA) in a planetary mixer (ARE310, THINKY, Japan) for 4 min at 1500 rpm, and cured in the molds in a VWR forced air oven (Avantor, Radnor, PA, USA) at 80°C for 2 h. The casts were extracted, trimmed, and fitted and traced onto a 3 mm suit worn by the diver (Figure 1E, F, G). Thin neoprene pieces were cut to match the tracings and glued to the suit using neoprene cement, thereby encapsulating the composite segments and attaching them to the 3 mm suit in watertight external pockets. This completed the assembly of the K-suit.

Preliminary field tests were conducted by a pair of divers in Monterey Bay, wherein one diver wore the K-suit and the other a commercial 7 mm neoprene suit (AquaLung, Vista, CA, USA). Both were trained US Navy divers and Naval Postgraduate School students, with muscular builds and in excellent physical shape and health. Biometric data for the two divers are shown in Table 1.

Figure 2

Field test results; the K-suit wearer (blue datapoints) dived with a buddy wearing a commercial 7 mm neoprene suit (orange datapoints) in salt water in Monterey Bay at ~10°C. Both divers wore automated dataloggers inside and outside the suits, recording temperature and pressure. The temperature delta between the inside and outside for each diver, and the difference between the two deltas (grey datapoints) (A) and the corresponding depths (B) are plotted against time since the start of the dive



The temperature of the salt water was ~10°C and the diving depth was up to 10 msw. Pressure and temperature were recorded by OM-CP-PRTEMP1000 automated dataloggers (Omega Engineering, Norwalk, CT, USA). Each diver wore one logger between his suit and his breastbone, and one on the outside attached to his buoyancy control device. Loggers digitally recorded temperature and pressure at 0.1 s intervals. After the dive, the watertight caps on the loggers were unscrewed to access the USB ports and the data were downloaded.

Results

Figure 2 shows the field test results. Figure 2A shows the temperature difference (inside minus outside) for each diver over time since the start of the dive. Figure 2B shows the depth of each diver as calculated from the pressure data. The time start is at the beginning of the dive.

These data suggest that the standard 7 mm neoprene suit leads to a quicker drop of temperature difference compared to the K-suit. The results also show that the K-suit maintains about +4°C higher temperature difference compared to the 7 mm suit, as indicated by the delta of the differences on the same plot.

In terms of ergonomics, the K-suit wearer felt that the K-suit had the same ease of movement as a 3 mm neoprene suit, i.e., a significant improvement compared to a 7 mm suit. On the other hand, added difficulty was experienced in donning and doffing the K-suit.

Discussion

Figure 2B reveals the neoprene wearer spent more time at shallower depth than the K-suit wearer. It is known that neoprene insulation worsens with depth.[9] In addition, the K-suit wearer was shorter, lighter, and with lower BMI than the neoprene wearer (see Table 1). Therefore, he had a higher surface-to-volume ratio and lower thermal capacity, and was at a disadvantage in thermal performance. These observations suggest the K-suit thermal advantage may be larger than Figure 2A suggests, but definitive conclusions would require a proper study with a larger number of subjects. Indeed, while these preliminary results represent a proof-of-concept, more subjects and dives would allow appropriate statistical analysis. The physical differences between divers would be better accounted for by alternating the wearing of the K-suit and neoprene.

The added donning/doffing difficulty of the K-suit is chiefly attributed to design that is yet to be perfected. For example,

the inclusion of pleated cuffs with zippers on the wrists and ankles ought to help solve the problem satisfactorily. Similar pleating can be included in other areas as needed. Ergonomics improvements must be studied quantitatively.

Future work would complete the K-suit's composite coverage by adding segments for the head, upper arms, and lower arms, and then field testing with analogous methodology. Diving longer, at greater depths and in colder waters would quantify any advantage in colder environments. The loggers would be replaced with thermistors at multiple sites on the skin of the divers.

Conclusions

We have presented a novel segmented composite diving suit called the 'K-suit'. A single, preliminary field test suggested the K-suit outperforms a commercial 7 mm neoprene suit in both thermal protection and ergonomics. Hence, the K-suit has high potential practical utility and promise. The thermal and ergonomics superiority of the K-suit, combined with its relatively easy and inexpensive manufacture, could be of great practical utility to the military, professional and recreational diver communities, but definitive conclusions require further study.

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Case reports

Haemoptysis in breath-hold divers; where does it come from?

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Key words
Bronchoscopy; Case reports; Freediving; Hemoptysis; Pulmonary barotrauma; Pulmonary oedema

Abstract

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Introduction: The aim of reporting these two cases is to present visual evidence by bronchoscopy of the origin of haemoptysis in two elite breath-hold divers.
Case reports: Two male elite breath-hold divers of similar physical characteristics presented to our clinic after performing dives of up to 75 and 59 meters of seawater depth for 2:30 and 2:35 (minutes:seconds) respectively. Both patients presented with haemoptysis. Lung ultrasound was performed. The first patient had crackles on chest auscultation, overt pulmonary oedema clinically and 90 ultrasound lung comets. The second patient had no oedema or crackles, but presented with 20 ultrasound lung comets. Video bronchoscopy was performed which showed traces of blood coming from all three segments of the right upper lobe in both patients. The rest of the airways and lungs were intact.
Conclusions: These finding suggest that the apical parts of the lungs are the most prone to deep-dive induced damage. The precise mechanism of lung barotrauma and haemoptysis in breath-hold divers remains to be elucidated. These findings may be of importance for a better understanding of the underlying pathology of haemoptysis.

Introduction

Breath-hold diving is an extreme sport in which people may dive to substantial depths without any breathing equipment. Breath-hold divers (BHD) may suffer from pulmonary oedema, haemoptysis and chest pain after performing moderate to deep dives. There are case reports that describe these events; however, to date none report examination by bronchoscopy immediately after diving to definitively localise the source of active bleeding.[1]

The mechanism of pulmonary complications in deep BHDs remains unclear so the aim of this case report was to present two cases of haemoptysis caused by breath-hold diving and to demonstrate the place of origin of this bleeding in the respiratory system.

BHDs are exposed to a unique physiological condition, which combines extreme ambient pressure with physical exercise under prolonged hypoxic conditions. As such, our study identifies the weakest structural point in the healthy adult lung, which may be of importance for the understanding of lung pathology associated with haemoptysis.

Case reports

Both divers consented to the publication of their case details.

Two male elite BHDs presented to our clinic on separate occasions for assessment and treatment for haemoptysis after deep breath-hold diving. Both patients had similar general characteristics. Patient 1 was 34-years-old, 185 cm tall, with a weight of 84 kg. The depth of his dive that day was 75 metres of seawater (msw) and the duration of the dive was 2:30 minutes. Patient 2 was 28-years-old, 181 cm tall and weighed 85 kg. His dive was up to 59 msw and lasted 2:35 minutes.

Both divers had spirometry and plethysmography measurements before the incident dives during regular

medical checkups. Total lung capacity (TLC) and residual volume (RV) were taken as means of three measurements. For Patient 1, TLC was 9.56 L and RV 2.12 L. For Patient 2, TLC was 10.55 L and RV 2.58 L. According to Boyle-Mariotte's law (Volume = 1 / Pressure), TLC at maximal depth for both BHDs was less than RV at the surface.

Both patients were admitted to the Emergency Department of the Clinical Medical Centre in Rijeka around three hours after their last dives and were immediately examined by a pulmonologist. The first patient remained dyspnoeic during low level of exertion, and had haemoptysis and pulmonary crackles on chest auscultation. The second patient had symptoms immediately after the dive but they had resolved before arrival to hospital and chest auscultation was normal. Hospital admission was recommended to both patients but both refused.

Lung ultrasound was performed with a GE LogicV convex probe (3.5 to 5 Mhz) (GE Healthcare, Chicago, IL, USA) on both divers to detect extravascular lung water by counting the number of B-lines or ultrasound lung comets (ULCs).[2] The ULC is defined as an echogenic, coherent, wedge-shaped signal with narrow origin arising from the pleural line and extending to the far edge of the viewing area.[3] Sixty-one predetermined chest sites were used to calculate ULC and the sum of all scanning areas was recorded.[4] The first of the two patients who had crackles on chest auscultation and clinically overt pulmonary oedema had 90 ULCs. In the right apical area atelectasis was observed. The second patient had 20 ULCs and no signs of pulmonary oedema. It was hypothesized that more ULCs had been present, but were mostly resolved since the dive, as has been described previously.[4,5]

Video bronchoscopy was performed with an Olympus Bf-1T180 fibreoptic bronchoscope (Olympus Medical Systems, Tokyo, Japan) around 3.5 h after the last dive for both divers. In both divers traces of blood coming from all three segments of the right upper lobe (RUL) bronchus were visualised (Figures 1 and 2). The upper airway and trachea as well as the left bronchial tree and the right middle and lower lobe of the lungs were normal in appearance in both divers.

Discussion

Lung barotrauma arising from compression and its symptoms such as haemoptysis and lung oedema have been described in breath-hold divers before;[6] however, the anatomic origin of the blood and the cause of these symptoms remains unclear.

The current explanation of these phenomena is a combination of cardiovascular changes during immersion, increased hydrostatic pressure and apnoea. During breath-hold diving, the ambient pressure increases proportionally with depth and the volume of air in the lungs decreases (Boyle-Mariotte's law). When total lung capacity is reduced to residual volume, the volume of air in the lungs cannot decrease anymore and a further increase in ambient pressure will result in negative pressure in the thorax. This will increase blood shift to the thorax.[7] Immersion in water and apnoea induce an autonomic response that drives peripheral vasoconstriction

Figure 1
Blood found in patient 1 by video bronchoscopy in the right upper lobe of the lung, three and a half hours after performing a breath-hold dive lasting 2:30 minutes to 75 msw

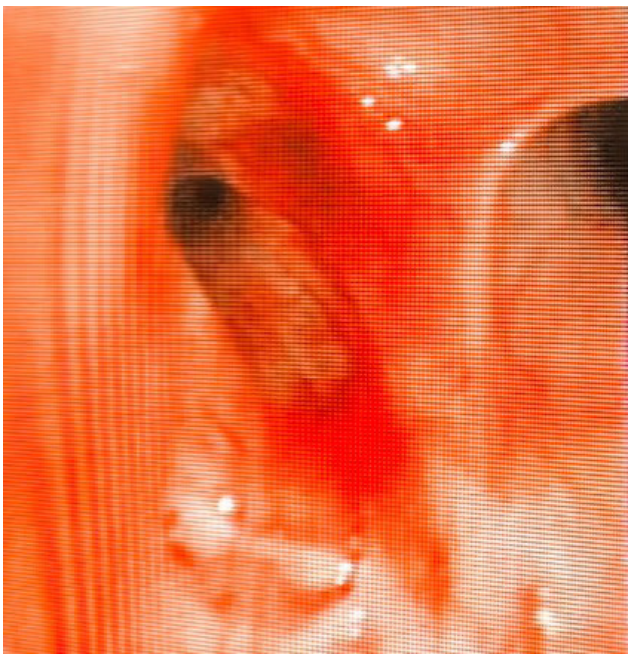
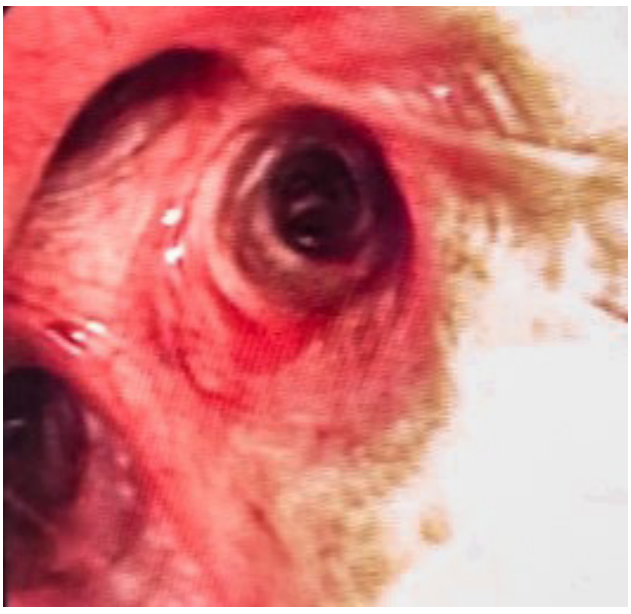


Figure 2
Blood found in patient 2 by video bronchoscopy in the right upper lobe of the lung, three and a half hours after performing a breath-hold dive lasting 2:35 minutes to 59 msw



and bradycardia.[8] Immersion also induces a 'buoyancy effect' on blood shift to the thorax as the effect of gravity is lost. Thus, immersion, increased hydrostatic pressure and apnoea cause a large blood shift to the thorax and significant pulmonary vascular engorgement. If pulmonary capillary pressure exceeds oncotic pressure, transudation from capillaries occurs and can lead to pulmonary oedema. Massive blood shift can significantly increase transmural pulmonary capillary pressure. In addition, negative pressure in the alveoli can increase transcapillary pressure and possibly result in endothelial damage and stress-induced capillary failure.[9]

Lung oedema in BH divers has previously been confirmed with X-ray,[10] computed tomography,[11] ultrasound[4] and pulmonary function tests.[12] There have been case reports of haemoptysis in which bronchoscopy with bronchoalveolar lavage was done but only several days after admission to hospital. One study confirmed haemoptysis in breath-hold divers with laryngoscopy and showed that the bleeding had its origin below the vocal cords.[12] Direct visualisation of bleeding during haemoptysis had not previously been described. We now show that traces of blood were visualised with a bronchoscope coming from all three segments of the right upper lobe bronchus following deep-dives.

These findings pose the question why the right upper lobe is the origin of the bleeding in both divers. It is true that the lung has a vertical difference of pleural pressure and there has been no research into how human lungs compress, collapse and re-expand under high pressure. Such research would be very difficult to obtain underwater and could be potentially dangerous to BHDs. One study reported a computational model of the mechanics of airway and alveolar collapse in humans during deep dives.[13] Lung mechanics under pressure cannot be determined by applying Boyle-Mariotte's law alone, because lungs and airways differ in structure, compliance, perfusion and surfactant over their various anatomical regions and will not collapse and reopen equally. One study found a lack of ventilation in several apical regions of divers' lungs when a small volume was inhaled after below residual volume exhalation in healthy subjects at sea level, which could also point towards the idea that apical parts of the lungs are the first to collapse.[14]

The paranasal sinuses have very little compliance, and their volume will remain almost constant throughout a dive. The mouth and supraglottic compartments are very compliant and will collapse and reopen without consequences, tracheal volume will decrease by inward invagination of its flexible posterior wall, and the anterior part will compress to a smaller extent. The small airways are more compliant than alveoli and will collapse prior to alveoli. Autonomic regulation of smooth muscle cells in the lower airways has an important role in controlling compliance and at the same time collapse and reopening of the alveoli. During breath-hold diving the airway pressure will remain the same throughout the lungs and airway but pleural pressure will depend on body position. If a diver dives head-first, the highest pleural pressure will be in apical parts of the lungs and apical alveoli will shrink faster.[13] As a result, their closing volume will be reached at shallower depth than for basal alveoli. When the diver reaches maximal depth, turns and ascends head towards surface apical alveoli will be under the lowest pleural pressure and will tend to re-open. Reopening of closed alveoli does not happen simultaneously in a homogenous pattern.[13]

Conclusion

To our knowledge this is the first report in which the exact part of the airway where bleeding originates in pulmonary barotrauma of compression ('lung squeeze') has been identified. Both of these divers had blood in the RUL bronchus; other parts of upper airways and lungs were normal in appearance. We conclude that in healthy adult lungs, the apical parts of the right lobe may be the most vulnerable to deep-dive induced stress. The precise mechanism of lung squeeze and haemoptysis in BHDs remains to be elucidated. Our findings may be of importance for a better understanding of pathologies associated with haemoptysis.

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Air embolism during lumbar surgery in the prone position

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Key words
Anaesthesia; Case reports; Cerebral arterial gas embolism (CAGE); Hyperbaric oxygen treatment; Neurosurgery; Surgery

Abstract

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Only a few clinical cases of cerebral arterial gas embolism during spinal surgery are published. It seems important not to overlook this diagnosis in order to initiate rapid appropriate treatment. This was a suspected case of paradoxical gas embolism revealed postoperatively by neurological deficits and whose recovery was noted during hyperbaric oxygen treatment. Unfortunately, no complementary examination showed gas embolism and only the context, the clinical picture and the case evolution evoke this diagnosis. The diagnostic difficulty in the immediate postoperative period is highlighted.

Introduction

During lumbar surgery in the prone position, air embolism (AE) can occur and is likely underdiagnosed.[1] There are only a few reports of such a complication.[2] Interestingly, reported cases are typically fatal but AE can also occur with various clinical presentations. Therefore, this clinical scenario is important, as is early diagnosis of AE in this unusual context in order to be able to initiate appropriate treatment as early as possible. Herein is reported a probable case of a cerebral arterial gas embolism (CAGE) during lumbar spine surgery. To our knowledge, this is the only case of CAGE revealed by neurological deficits after lumbar spine surgery with a rapid and complete recovery after hyperbaric oxygen treatment.

Case report

The patient consented to publication of his case details.

A 62-year-old ,76 kg male patient with history of hypertension and type 2 diabetes mellitus treated with oral medications, presented for elective L4-5 laminectomy surgery. He had previously been operated on without any complication. Preoperatively, the patient was alert and did not have any neurological deficit.

General anaesthesia was conducted with total intravenous anaesthesia with a targeted controlled infusion of propofol and sufentanil. Boluses of ketamine and lidocaine were administered at the beginning of the procedure, and rocuronium was given prior to orotracheal intubation. The patient was then placed in a knee-chest prone position. Standard monitoring (electrocardiogram, non-invasive arterial blood pressure, pulse oximetry, end-tidal CO_2 [E_TCO_2]) was used during anaesthesia. The surgery lasted 115 minutes and the blood loss was estimated to be 100 mL. The arterial blood pressure was maintained using continuous infusion of norepinephrine. No adverse change in the electrocardiogram, hypotension, or fall in E_TCO_2 was observed during the surgery. Only one transient mild arterial oxygen desaturation (from 99% to 96%) was recorded. The patient received tramadol, nefopam, and paracetamol for post-operative analgesia. At the end of the procedure, the train-of-four indicated the presence of four twitches with T4/T1 of 99%. A mild desaturation (SpO_2 = 94% with FiO_2 = 70%) that lasted a few minutes was managed by a recruitment manoeuvre. The patient was subsequently extubated (76 min after the end of the surgery).

On emergence, he was extremely agitated; his restlessness was attributed to the post-operative back pain which was treated with a 1mg intravenous bolus of morphine. Soon after the injection the patient became stuporous. The examination revealed an anisocoria, right hemiplegia, and bradypnoea with a stable heart rate, blood pressure, and temperature. Shortly after, re-examination revealed that anisocoria and hemiplegia had resolved. However, due to progressive respiratory distress not responsive to naloxone and a decreasing level of consciousness, the patient was re-intubated (1 hour after the prior extubation). He was extubated again 103 min later, but was still agitated, aphasic, with mild tetraparesis.

A brain magnetic resonance imaging (MRI) with contrast injection (FLAIR, T2*, diffusion and perfusion weighted imaging, 3D, time of flight, and contrast-enhanced MR angiography sequences of the supra-aortic vessels) was performed urgently (5 h after the end of the surgery) and

revealed no sign of stroke. Upon re-examination, the patient had dysarthria, hyperreflexia and a severe tetraparesis; the NIH Stroke Scale scored was 21. The blood serum chemistry was normal. Faced with this picture of unexplained polymorphic neurological failure, a CAGE was suspected and the patient was placed in a hyperbaric chamber. He underwent a 180-min session of HELIOX B30 (compression to 405.2 kPa [four atmospheres absolute] breathing a 60% oxygen–40% helium mixture), 9 h after the end of surgery. Thirty minutes after the beginning of the session the patient displayed an improvement in phasic disorders and partial recovery of his tetraparesis. At the end of the session, the phasic disturbances had disappeared and a mild tetraparesis persisted. The symptoms were completely resolved a few hours later after the patient returned to the ward.

Discussion

Gas embolism refers to the entry of gas (often air) into the vasculature, which requires a pressure gradient favouring the passage of the gas in the blood vessel. In surgery this can occur particularly in sitting position but the risk of gras entrainment (particularly into the venous circulation) exists any time the operating site is above the level of the heart. During the prone position two factors can contribute to an AE: a gravitational gradient between the heart and the operative site, and a negative pressure within the epidural veins secondary to the decompression of the abdomen.[1] Air bubbles can then migrate into the systemic circulation via physiologic shunts or incomplete filtration by the pulmonary capillaries,[3] also called paradoxical air embolism. When bubbles reach the cerebral vasculature (i.e., CAGE), they may cause variable neurological symptoms from a sudden change in sensorium to disorientation or coma, mimicking an ischaemic stroke.[4] Although the neurological symptoms most commonly result from cerebral focal ischaemia and oedema from air emboli lodged in small cerebral arteries, these bubbles also induce an inflammatory process damaging the endothelial cells of the vessel wall. As with sitting surgery, surgery in the prone position is likely to have a higher than reported incidence of micro paradoxical embolism. However, the clinical significance of micro-CAGE is not clear.[5]

The outcome of CAGE depends on the diagnosis and treatment delays, which should be as short as possible. During the post-operative period, the early recognition of symptoms is difficult due to the confounding effects of anaesthesia. The motor deficit can be due to a residual muscle relaxation or a metabolic disturbance; the restlessness to pain or a bladder retention or drug side effects; the decrease in alertness to residual drug effects; and the pupillary anomaly to some drug side effects or an ischaemic optic neuropathy. In any case, a surgical complication must always be considered. However, certain intraoperative observations, such as unexplained sudden hemodynamic or respiratory failure or a fall of E_TCO_2, should raise a flag whenever the procedure is being performed in a risky position. CAGE can be responsible for various neurological disorders such as headache, alterations in consciousness, seizures, focal or multi-focal motor deficit, pyramidal syndrome, cranial nerve deficit, visual disorders, sensory disorders, and phasic disorders. Its onset is abrupt but its clinical expression may vary over time. It may also be associated with respiratory and/or haemodynamic signs such as pulmonary oedema, acute respiratory distress syndrome, tachycardia, ST segment changes, right heart failure, or cardiac arrest.[6] A high suspicion of AE is thus sufficient to justify treatment. Sometimes diagnosis of CAGE (by directly visualising vascular gas) can be made using cerebral imaging (computed tomography or MRI). However, air bubbles can be partially resorbed within the first hours, and the presence of air can no longer be demonstrated using brain imaging. Therefore, normal imaging should not exclude a diagnosis of CAGE.[7]

Recovery from CAGE can be spontaneous as reported in many cases but the use of hyperbaric oxygen is the treatment of choice,[8] as it decreases bubble size and increases oxygen solubility in plasma.[9] Access to a hyperbaric medicine centre can be the limiting factor for this treatment. Although hyperbaric oxygen treatment should be started as soon as possible there have been reports of significant clinical improvement even after considerable delays in treatment.[10] In the case presented here, once other differential diagnoses such as residual muscle relaxation, metabolic disturbances, ischaemic or haemorrhagic stroke were ruled out, the most plausible diagnosis was CAGE . Other differential diagnoses were mentioned and were not completely excluded (i.e., drug overdose, acute anticholinergic syndrome), although the clinical features were hardly compatible. Moreover, the rapid favourable evolution during hyperbaric oxygen treatment supported the CAGE hypothesis.

Conclusions

CAGE is a serious and often fatal event that can occur in every procedure at risk, i.e., when a pressure gradient favours the passage of the gas in a blood vessel. Due to the lack of symptom specificity, a high index of suspicion should be maintained to allow for prompt diagnosis and rapid treatment of the condition, and ultimately rapid recovery and reduced morbidity.

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Conflicts of interest and funding: nil

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Letter to the Editor

Anxiety impact on scuba performance

We are concerned about the scientific validity of a recent paper on the impact of anxiety on scuba performance[1] on the following basis:

1. In their analyses men and women were grouped together, whereas the two sexes should have been analysed separately. The chi-square comparing male:female/high:low anxiety produced the same *P*-value (0.15) as that reported, but the small female/low anxiety group (only three subjects) makes the result unreliable statistically. Therefore, one cannot be sure that there are no sex effects. If this initial assumption that there is no significant difference between the sexes cannot be relied upon, then this has a knock-on effect to all further analyses and to any inferences drawn.

2. It is unclear why the authors used the State-Trait Anxiety Inventory to measure only individual trait anxiety. Measuring individual 'State anxiety' immediately prior to the experimental trials would have been a more relevant test. The assumption that Trait anxiety measures provide an *a priori* threshold for the prediction of panic behaviour is based on the findings of a single study of novice scuba students undertaking a training course.[1] In the present study, the participants were certified open-water or advanced open-water divers, including one qualified rescue diver. Therefore, this is not an appropriate or true comparison. Also, whilst susceptibility to panic is associated with increased Trait anxiety, women are twice as susceptible to panic as men.[2] It is proposed that this sex-specific vulnerability arises due to an interaction with changes occurring during the premenstrual phase of the menstrual cycle.[3]

3. Submerging to 5 metres of fresh water in an outdoor pool is unlikely to be anxiety provoking with this cohort. Even those recording a high level of 'Trait anxiety' may be showing a low level of 'State anxiety' at the time of the dive; indeed, some may even have found it relaxing. Consequently, the statement that "*…this study sought to confirm the following issues: (1) whether anxious divers would exhibit slower diving skills performance; (2) whether anxious divers would have inefficient cognitive processing ability in underwater conditions;…*" is not supported without measuring State anxiety immediately prior to the experimental phases.

4. A previous study found no impairment in inhibitory control using Stroop at a depth of 5 m although it was observed at a depth of 20 m.[4] The finding of impairment in inhibitory control may, therefore, be due to sex differences rather than Trait anxiety. Furthermore, the effects of anxiety on performance may be modulated by sex.[5,6] Unfortunately there is no published research on sex differences in diver performance. In some other situations, highly anxious women outperform men; in other cases, men outperform women and at times there is no difference in performance. Also population distribution may be skewed with one group showing a normal distribution whilst the other may have either an unimodal or bimodal distribution. Recent work (by JL, unpublished) on differences in behaviour between men and women in survival situations suggests that men tend to show a more or less normal distribution and women a more bimodal distribution in coping ability. There can also be within-population differences amongst women given that the menstrual cycle can mediate State anxiety in its effect on cognitive function.[3] Differences in fear and anxiety between men and women are complex issues influenced by a broad range of factors.[2]

5. The Stroop test cannot be used reliably as a sole measure of executive function, let alone cognitive function. Whilst it does measure interference control, which is a sub-component of executive function, there are other sub-components to be considered. One author (JL) has found in his own work that duress affects these sub-components differentially;[7] in other words, not all subcomponents of executive function are impaired under the same conditions.

In summary, the authors should consider retracting their paper on the grounds that, most importantly, the sex/anxiety premise is unsound, given the unreliable initial chi-square analysis, and the knock-on implications of this to the rest of the analyses. Secondly, what is concluded does not provide any new contribution to the field. To study possible sex differences in task performance (mask clearing, buddy breathing, etc.) either to eliminate them or to identify possible differential effects would require an appropriate-sized (larger) study sample. Either that or the study cohort should have been of only one sex.

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Editorial note

The authors of reference 1 were invited to reply to this letter, but did not respond. If a response is forthcoming it will be published in a subsequent issue.

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Letters (to the Editor); Performance; Personality; Psychology; Recreational diving; Stress; Women

doi: 10.28920/dhm51.3.306-307. PMID: 34547784.

Notices and news

EUBS notices and news and all other society information can be found on:
https://www.eubs.org/

EUBS President's message

Ole Hyldegaard

As we approach a virtual general assembly in September with online voting similar to last year, this will be, unfortunately, my last message to DHM as your EUBS President. When we all last met in Tel-Aviv 2019, little did we know what the following two years would bring, certainly not a pandemic situation requiring a lockdown of all our physically related activities. These circumstances mean that we should embrace and appreciate our annual, physical and social gatherings at our annual scientific meetings all the more. We have all realised the importance of our annual face-to-face EUBS meeting, during these times when we are prevented from holding them. This is indeed, something to look forward to once we will be able to interact again, hopefully next year in Prague for the EUBS 2022 annual scientific meeting.

Nevertheless, our society has continued to function and new challenges in both the professional diving industry, the recreational diving sector and the clinical world of hyperbaric medicine have emerged. Oxygen, as a drug, has been given new interest, feeding new research projects and insights into our understanding of how oxygen works as part of basic metabolism, inflammation, infection regulation and tissue rebuilding. There is still so much research to be done and clinical testing to be performed.

Although these are unusual times, it has been a pleasure to be part of the EUBS ExCom, the work of the society and our joint scientific journal of the EUBS and SPUMS societies.

A warm congratulations to Dr Bengüsu Mirasoğlu as incoming new Vice-President Elect of the EUBS and to Dr Evangelos Papoutsidakis as newly elected Member-at-Large of the EUBS ExCom. A special thank you to Dr med. François Guerrero for his work on the EUBS ExCom since 2018, he now leaves the committee. A warm thank you for the willingness and support from our good colleagues Charles P Azzopardi, José M Inoriza and Mario Franolic for participating in the elections for Member-at-Large for the EUBS ExCom. With these words, I look forward to continuing work within EUBS ExCom and send a warm welcome to my successor Dr Jean Eric Blatteau as our new EUBS President.

Stay safe and warm greetings to all EUBS members!

Ole Hyldegaard
EUBS President

EUBS Notices and news

EUBS Member-at-Large elections

Each year between June and August, the EUBS membership elects a new Member-at-Large, and Dr med. François Guerrero will leave office as Member-at-Large 2018. Dr Evangelos N Papoutsidakis, working at the Department of Hyperbaric Oxygen of the CRIS-UTH, Hospital Moisses Brogges, Sant Joan Despi in Barcelona (Spain), has been elected by the EUBS members as our new Member-at-Large, for the 2021–2023 term. The ExCom extend their thanks to François Guerrero for his work in ExCom, and we all hope he will remain active for the Society.

Almost 60% of our members voted, and the EUBS ExCom would like to thank the other candidates for this position (Charles P Azzopardi, Mario Franolic and José M Inoriza) for their willingness to serve the Society, and encourage them to not be disappointed by the voting result.

We have also elected a new Vice-President, who will take on a prominent position in our Society. Dr Bengusu Mirasoglu, who has served in our ExCom as a Member-at-Large before, will be our new Vice-President after our General Assembly. Professor Jean-Eric Blatteau will take over as President and Professor Ole Hyldegaard will become Past President.

Thanks to all EUBS members who have voted, and please, if you have any comments on the voting process or software used, send us an email secretary@eubs.org.

EUBS 2020 – Postponed to 2022

Due to the COVID-19 pandemic, our 2020 Annual Scientific Meeting could not take place, and also, our plans for 2021 have had to be postponed. It has been decided by ExCom to postpone our Annual Scientific Meeting yet again and thus,

our 2022 EUBS Annual Scientific Meeting will (finally?) take place in Prague, Czech Republic, in September 2022 (exact dates to be confirmed).

The meeting will be organised by a Local Organising Committee chaired by Michal Hajek, M.D., Ph.D., a long-time member of EUBS, and member of Executive Board of ECHM; in collaboration with the Czech Society of Hyperbaric and Aviation Medicine, the City Hospital of Ostrava, the Faculty of Medicine of Ostrava University, the Faculty of Medicine of Charles University in Hradec Kralove, the Cochrane Institute Czech Republic, The Czech Republic (Middle European) Centre for Evidence-Based Healthcare: The Joanna Briggs Institute Centre of Excellence, the Masaryk University GRADE Centre, DAN Europe, and others.

Hyperbaric medicine has a long tradition in Czech Republic – in 2020 it was 55 years since that field of medicine in this country was established.

It is hoped and expected that by then, 'real life meetings' will again be possible, as they provide the salt and pepper of scientific work and allow direct, informal contacts in a relaxed atmosphere. So please keep September 2022 free for Prague!

EUBS General Assembly

As our Annual Scientific Meeting has been postponed to 2022 (see above) we will again not be able to hold a General Assembly (GA) 'in person' this year. EUBS ExCom has considered the various options for holding a virtual GA and, just like last year, we propose the following procedure:

1 By the time this issue of DHM appears, EUBS ExCom will already have held their 'pre-Annual Meeting' ExCom meeting online, to prepare a GA document, much like the 'live' GA document; this will be sent to all members and will relay the necessary/useful information to all members.
2 We will prepare internet voting using the ElectionRunner software (the same software used for the yearly EUBS ExCom Elections). Each item that needs a vote from the EUBS Membership will be formulated as a 'yes' or 'no' question and the relevant information will be added in the voting app (so that you will not necessarily need to have the first document at hand to decide).
3 We will restrict the GA voting to items of current matters only. We will allow for at least two weeks to vote.

EUBS website

As always, please visit the EUBS website (www.eubs.org) for the latest news and updates. Do not forget to renew your membership annually – each member will receive a personal renewal invitation one month before expiry; even if your membership has expired, you can easily renew it when trying to log in again. In case of problems, do not hesitate to contact the EUBS secretary at secretary@eubs.org.

EUBS website and OXYNET

Occasionally, we can use the EUBS website newsletter as a tool to seek help for our members, as it is a perfect way to reach all of the EUBS membership and because communication, networking and interaction are prime goals of our society.

The OXYNET database of hyperbaric centres has been compiled and verified as good as possible by ExCom members Rodrigue Pignel and Bengusu Mirasoglu last year, and is now presented as an interactive map page on the EUBS website.

A Help Requests page on our EUBS website has been created (EUBS Members Help Requests, under the 'Activities' menu on the homepage). Please check this page and try to help out. In case you need help as well and would like to use this service, please contact the webmaster (webmaster@eubs.org).You should also consult the page where research projects seeking collaborators and international participation are presented.

Notices and news

SPUMS notices and news and all other society information can be found on:
https://spums.org.au/

SPUMS President's message

Neil Banham

I have just returned from the Cocos Keeling Islands (an Indian Ocean Territory of Australia), a tiny atoll in the Indian Ocean far to the west of Western Australia and closer to Indonesia than the Australian mainland. The Cocos Islands have a tropical climate with wonderful snorkelling and diving, but unfortunately lack sufficient infrastructure and diving capacity to support a future SPUMS Annual Scientific Meeting (ASM).

Since my last report, the highly successful, if not unconventional SPUMS ASM at HMAS Penguin was held both virtually and in-person for those fortunate enough to be able to travel to Sydney. I was not one of those, but was able to watch all presentations in the comfort of my own home. Many thanks to the Convenor Doug Falconer and to our invited speaker Dr Richard Harris SC, OAM, and to all others who participated as either speakers and/or delegates. The planning for our 2022 ASM is continuing, and will most likely be in New Zealand. Whether or not this will be in Tutukaka and include diving, or be a mix of virtual and in person attendance in Auckland, is still being decided. Look out for details on our website https://spums.org.au/.

Promisingly, increasing rates of COVID-19 vaccination mean that overseas travel to scientific meetings (and diving!) may soon be possible, and as such, both UHMS and EUBS are also planning their ASMs for 2022. Perhaps SPUMS will be able to hold the 2023 ASM in a suitably tropical destination! I strongly encourage you all to be active advocates for COVID-19 vaccination.

The ANZHMG Introductory Course in Diving and Hyperbaric Medicine was able to be completed immediately following the SPUMS ASM and was again held in Fremantle, Western Australia. The course was highly successful and received great feedback from participants. Many thanks to the Convenor Ian Gawthrope and to all who contributed. The next course is planned for 21 February – 04 March 2022, again in Fremantle. Details can be found at https://www.spums.org.au/content/approved-courses-doctors.

The SPUMS Medical will be completely updated by the end of 2021, complementing the revision to the Cardiovascular fitness-to-dive published in 2020. This major revision is being coordinated by Clinical Professor David Smart and a small group of ExCom volunteers and will be posted on the SPUMS website when complete.

Finally, these are challenging times for societies because of reduced opportunities for travel for professional development, and there is a real risk that SPUMS membership numbers will fall; hence a plea to all members to renew their membership again this year and also to recruit others whom they know with an interest in diving medicine.

Neil Banham
SPUMS President

Errata

In the last issue of *Diving and Hyperbaric Medicine*, SPUMS notices and news, it was reported in the ANZHMG Chair's report that Dr Emma Tucker from Tasmania was awarded the Unsworth Prize. Bob Webb the Chairperson was given the incorrect name for his report and the correct recipient of the award is Dr Emma Wilson. We apologise to Dr Wilson for this error and wish her congratulations.

The SPUMS website is at
https://spums.org.au/

Members are encouraged to log in and keep their personal details up to date.

The latest issues of *Diving and Hyperbaric Medicine* are via your society website login.

Government of **Western Australia**
South Metropolitan Health Service
Fiona Stanley Fremantle Hospitals Group

The Australian and New Zealand Hyperbaric Medicine Group

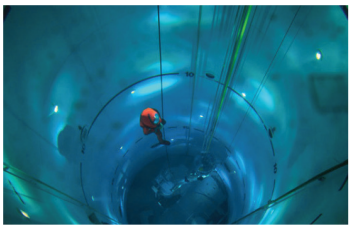
Introductory Course in Diving and Hyperbaric Medicine

Dates: 21st Feb – 04th Mar 2022
Venue: Hougoumont Hotel, Fremantle, Western Australia
Cost: AUD 2,700 for 2 weeks

The course is for medical graduates with an interest in diving and hyperbaric medicine. It is designed both for those wishing to pursue a career in this specialised field and those whose primary interest lies in related areas. The course will be held in Fremantle with excursions to the Fiona Stanley Hyperbaric Medicine Unit, HMAS Stirling and the local Royal Flying Doctor base. The course is accredited with the South Pacific Underwater Medicine Society and ANZCA for the Diploma of Diving and Hyperbaric Medicine.

The Course content includes:

- History of diving medicine and hyperbaric oxygen
- Physics and physiology of diving and compressed gases
- Presentation, diagnosis and management of diving injuries
- Assessment of fitness to dive
- Visit to RFDS base for flying and diving workshop
- Accepted indications for hyperbaric oxygen treatment
- Hyperbaric oxygen evidence based medicine
- Wound management and transcutaneous oximetry
- In water rescue and management of a seriously ill diver
- Visit to HMAS Stirling
- Practical workshops
- Marine Envenomation



Contact for information:

Sue Conlon, Course Administrator
Phone: +61-(0)8-6152-5222
Fax: +61-(0)8-6152-4943
E-mail: fsh.hyperbaric@health.wa.gov.au
Accommodation information can be provided on request

FSHM20190523004

Royal Australian Navy Medical Officers' Underwater Medicine Course 2021

Date: 01–12 November 2021 and 14–25 March 2022

Venue: HMAS Penguin, Sydney

The MOUM course seeks to provide the medical practitioner with an understanding of the range of potential medical problems faced by divers. Emphasis is placed on the contraindications to diving and the diving medical assessment, together with the pathophysiology, diagnosis and management of common diving-related illnesses. The course includes scenario-based simulation focusing on the management of diving emergencies and workshops covering the key components of the diving medical.

Cost: The course cost remains at AUD$1,355.00 (ex GST), this is yet to be confirmed.

For information and application forms contact:
Rajeev Karekar, for Officer in Charge
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HMAS Penguin
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Email: *rajeev.karekar@defence.gov.au*

Australian and New Zealand College of Anaesthetists Diving and Hyperbaric Medicine Special Interest Group

The new Diploma of Advanced Diving and Hyperbaric Medicine was launched on 31 July 2017. Those interested in training are directed to the ANZCA website https://www.anzca.edu.au/education-training/anzca-diploma-of-advanced-diving-and-hyperbaric-me.

Training
Documents to be found at this site are:

- Regulation 36, which provides for the conduct of training leading to the ANZCA Dip Adv DHM, and the continuing professional development requirements for diplomats and holders of the ANZCA Certificate of DHM;
- ANZCA Advanced DHM Curriculum which defines the required learning, teaching and assessment of the diploma training programme; and
- ANZCA Handbook for Advanced DHM Training which sets out in detail the requirements expected of trainees and accredited units for training.

Examination dates for 2022

Written examination	See website for dates
Viva examination	See website for dates

Accreditation
The ANZCA Handbook for Advanced DHM accreditation, which provides information for units seeking accreditation, is awaiting approval by Standards Australia and cannot yet be accessed online. Currently six units are accredited for DHM training and these can be found on the College website.

Transition to new qualification
Transitional arrangements for holders of the ANZCA Certificate in Diving and Hyperbaric Medicine and highly experienced practitioners of DHM seeking recognition of prior experience lapsed on 31 January 2019.

All enquiries should be submitted to dhm@anzca.edu.au.

SPUMS Facebook page

Like us at:
http://www.facebook.com/pages/SPUMS-South-Pacific-Underwater-Medicine-Society/221855494509119

SPUMS Diploma in Diving and Hyperbaric Medicine

Requirements for candidates (May 2014)

In order for the Diploma of Diving and Hyperbaric Medicine to be awarded by the Society, the candidate must comply with the following conditions: They must

1 be medically qualified, and remain a current financial member of the Society at least until they have completed all requirements of the Diploma;
2 supply evidence of satisfactory completion of an examined two-week full-time course in diving and hyperbaric medicine at an approved facility. The list of such approved facilities may be found on the SPUMS website;
3 have completed the equivalent (as determined by the Education Officer) of at least six months' full-time clinical training in an approved Hyperbaric Medicine Unit;
4 submit a written proposal for research in a relevant area of underwater or hyperbaric medicine, in a standard format, for approval before commencing the research project;
5 produce, to the satisfaction of the Academic Board, a written report on the approved research project, in the form of a scientific paper suitable for publication. Accompanying this report should be a request to be considered for the SPUMS Diploma and supporting documentation for 1–4 above.

In the absence of other documentation, it will be assumed that the paper is to be submitted for publication in *Diving and Hyperbaric Medicine*. As such, the structure of the paper needs to broadly comply with the 'Instructions for authors' available on the SPUMS website https://spums.org.au/ or at https://www.dhmjournal.com/.

The paper may be submitted to journals other than *Diving and Hyperbaric Medicine*; however, even if published in another journal, the completed paper must be submitted to the Education Officer (EO) for assessment as a diploma paper. If the paper has been accepted for publication or published in another journal, then evidence of this should be provided.

The diploma paper will be assessed, and changes may be requested, before it is regarded to be of the standard required for award of the Diploma. Once completed to the reviewers' satisfaction, papers not already submitted to, or accepted by, other journals should be forwarded to the Editor of *Diving and Hyperbaric Medicine* for consideration. At this point the Diploma will be awarded, provided all other requirements are satisfied. Diploma projects submitted to *Diving and Hyperbaric Medicine* for consideration of publication will be subject to the Journal's own peer review process.

Additional information – prospective approval of projects is required

The candidate must contact the EO in writing (or email) to advise of their intended candidacy and to discuss the proposed topic of their research. A written research proposal must be submitted before commencement of the research project.

All research reports must clearly test a hypothesis. Original basic and clinical research are acceptable. Case series reports may be acceptable if thoroughly documented, subject to quantitative analysis and if the subject is extensively researched in detail. Reports of a single case are insufficient. Review articles may be acceptable if the world literature is thoroughly analysed and discussed and the subject has not recently been similarly reviewed. Previously published material will not be considered. It is expected that the research project and the written report will be primarily the work of the candidate, and that the candidate is the first author where there are more than one.

It is expected that all research will be conducted in accordance with the joint NHMRC/AVCC statement and guidelines on research practice, available at: www.nhmrc.gov.au/_files_nhmrc/publications/attachments/r39.pdf, or the equivalent requirement of the country in which the research is conducted. All research involving humans, including case series, or animals must be accompanied by documentary evidence of approval by an appropriate research ethics committee. Human studies must comply with the Declaration of Helsinki (1975, revised 2013). Clinical trials commenced after 2011 must have been registered at a recognised trial registry site such as the Australia and New Zealand Clinical Trials Registry http://www.anzctr.org.au/ and details of the registration provided in the accompanying letter. Studies using animals must comply with National Health and Medical Research Council Guidelines or their equivalent in the country in which the work was conducted.

The SPUMS Diploma will not be awarded until all requirements are completed. The individual components do not necessarily need to be completed in the order outlined above. However, it is mandatory that the research proposal is approved prior to commencing research.

Projects will be deemed to have lapsed if:

- the project is inactive for a period of three years, or
- the candidate fails to renew SPUMS Membership in any year after their Diploma project is registered (but not completed).

For unforeseen delays where the project will exceed three years, candidates must explain to the EO by email why they wish their diploma project to remain active, and a three-year extension may be approved. If there are extenuating circumstances why a candidate is unable to maintain financial membership, then these must be advised by email to the EO for consideration by the SPUMS Executive. If a project has lapsed, and the candidate wishes to continue with their DipDHM, then they must submit a new application as per these guidelines.

The Academic Board reserves the right to modify any of these requirements from time to time. As of October 2020, the SPUMS Academic Board consists of:

Associate Professor David Cooper, Education Officer, Hobart
Professor Simon Mitchell, Auckland

All enquiries and applications should be addressed to:
Associate Professor David Cooper
education@spums.org.au

Key words
Qualifications; Underwater medicine; Hyperbaric oxygen; Research; Medical society

Courses and meetings

Foundation of Diving Research, SDR

Saturday 26 March 2022, AMC, Amsterdam: Symposium to celebrate the 50 year anniversary of the Dutch Stichting Duik Research (SDR, Foundation of Diving Research).

Topics: 50 years research by SDR; diving cardiology; safety of professional diving; diving to perform coral biotope research and open sea under water archaeology; physiological adaptations of diving mammals. 4 cp.

Visit: http://www.duikresearch.org/ or http://www.diveresearch.org/
For more information: n.a.schellart@amsterdamumc.nl

Publications database of the German Diving and Hyperbaric Medical Society (GTÜM)

EUBS and SPUMS members are able to access the German Society's large database of publications in diving and hyperbaric medicine. EUBS members have had this access for many years. SPUMS members should log into the SPUMS website, click on 'Resources' then on 'GTÜM database' in the pull-down menu. In the new window, click on the link provided and enter the user name and password listed on the page that appears in order to access the database.

Historical Diving Society Australia - Pacific

P O Box 347, Dingley Village Victoria, 3172, Australia
Email: info@historicaldivingsociety.com.au
Website: https://www.historicaldivingsociety.com.au/

Scott Haldane Foundation

As an institute dedicated to education in diving medicine, the Scott Haldane Foundation (SHF) has organised more than 300 courses all over the world, over the past 28 years. SHF is targeting on an international audience with courses world wide.

Due to the COVID-19 pandemic some courses are rescheduled. Fortunately, we were able to find new dates for all postponed courses. Below are the upcoming SHF courses for the second half of 2021 and January 2022.

The courses Medical Examiner of Diver (part 1 and 2) and SHF indepth courses, as modules of the level 2d Diving Medicine Physician course, fully comply with the ECHM/EDTC curriculum for Level 1 and 2d respectively and are accredited by the European College of Baromedicine (ECB).

2021

01–02 October	Medical Examiner of Divers part 1 (level 1), Zeist, NL
07–09 October	Medical Examiner of Divers part 2 (level 1), Amsterdam Univ. Med. Centre, NL
October	Internship different types of diving (2d) Royal Dutch Navy-Den Helder, NL
26–27 November	28th In-depth course diving and mental health (2d), Zeist, NL
11 December	Refresher course the diving medical in practice, Amsterdam, NL
On request	Internship HBOt (level 2d certification) NL/Belgium

2022

22–29 January	Medical Examiner of Divers part 1 for ENT specialists, Bonaire

The course calendar will be supplemented regularly. For the latest information see: **www.scotthaldane.org.** Please also check the COVID-19 news update on this website for the latest schedule changes.

German Society for Diving and Hyperbaric Medicine (GTÜM)

An overview of basic and refresher courses in diving and hyperbaric medicine, accredited by GTÜM according to EDTC/ECHM curricula, can be found on the website: http://www.gtuem.org/212/Kurse_/_Termine/Kurse.html

Diving and Hyperbaric Medicine: Instructions for authors

Full version, updated August 2021

Diving and Hyperbaric Medicine (DHM) is the combined journal of the South Pacific Underwater Medicine Society (SPUMS) and the European Underwater and Baromedical Society (EUBS). It seeks to publish papers of high quality on all aspects of diving and hyperbaric medicine of interest to diving medical professionals, physicians of all specialties, scientists, members of the diving and hyperbaric industries, and divers. Manuscripts must be offered exclusively to *Diving and Hyperbaric Medicine*, unless clearly authenticated copyright exemption accompaniesthe manuscript. All manuscripts will be subject to peer review. Accepted contributions will also be subject to editing.

***Address*:** The Editor, Diving and Hyperbaric Medicine, Department of Anaesthesiology, University of Auckland, Private Bag 92019, Auckland 1142, New Zealand
***Email*:** editor@dhmjournal.com
***Phone: (mobile)*:** +64 (0)27 4141 212
***European Editor*:** euroeditor@dhmjournal.com
***Editorial Assistant*:** editorialassist@dhmjournal.com
***Journal information*:** info@dhmjournal.com

Contributions should be submitted electronically by following the link:
http://www.manuscriptmanager.net/dhm
There is on-screen help on the platform to assist authors as they assemble their submission. In order to submit, the corresponding author needs to create an 'account' with a user name and password (keep a record of these for subsequent use). The process of uploading the files related to the submission is simple and well described in the on-screen help provided the instructions are followed carefully. The submitting author must remain the same throughout the peer review process.

Types of articles

DHM welcomes contributions of the following types:

Original articles, Technical reports and Case series: up to 3,000 words is preferred, and no more than 30 references (excluded from word count). Longer articles will be considered. These articles should be subdivided into the following sections: an **Abstract** (subdivided into Introduction, Methods, Results and Conclusions) of no more than 250 words (excluded from word count), **Introduction, Methods, Results, Discussion, Conclusions, References, Acknowledgements**, **Funding** sources and any **Conflicts of interest**. **Legends/captions** for illustrations, figures and tables should be placed at the end of the text file.

Review articles: up to 5,000 words is preferred and a maximum of 50 references (excluded from word count); include an informative **Abstract** of no more than 300 words (excluded from total word count); structure of the article and abstract is at the author(s)' discretion.

Case reports, Short communications and **Work in progress** reports: maximum 1,500 words, and 20 references (excluded from word count); include an informative **Abstract** (structure at author's discretion) of no more than 200 words (excluded from word count).

Educational articles, Commentaries and C**onsensus reports** for occasional sections may vary in format and length, but should generally be a maximum of 2,000 words and 15 references (excluded from word count); include an informative **Abstract** of no more than 200 words (excluded from word count).

Letters to the Editor: maximum 600 words, plus one figure or table and five references.

The journal occasionally runs **'World as it is'** articles; a category into which articles of general interest, perhaps to divers rather than (or in addition to) physicians or scientists, may fall. This is particularly so if the article reports an investigation that is semi-scientific; that is, based on methodology that would not necessarily justify publication as an original study. Such articles should follow the length and reference count recommendations for an original article. The structure of such articles is flexible. The submission of an abstract is encouraged.

Formatting of manuscripts

All submissions must comply with the following requirements. Manuscripts not complying with these instructions will be suspended and returned to the author for correction before consideration. Guidance on structure for the different types of articles is given above.

Title page: Irrespective of article type, it must have a Title page which lists the title of the paper, all authors' names in full and their affiliations and provide full contact details for the first (and corresponding, if different) author(s).

ORCiD requirements: ORCiD An ORCiD is now required for all corresponding authors when submitting to *Diving and Hyperbaric* Medicine. The ORCiD must be entered into Manuscript Manager when submitting (the site will prompt you to create one if you do not have one). Please add your ORCiD to the title page of your manuscript.

What is an ORCiD? ORCID provides a persistent digital identifier (an ORCID iD) that you own and control, and that distinguishes you from every other researcher. You can connect your iD with your professional information

– affiliations, grants, publications, peer review, and more. You can use your iD to share your information with other systems, ensuring you get recognition for all your contributions, saving you time and hassle, and reducing the risk of errors. For more information see https://orcid.org/.

Key words: The title page must also list a maximum of seven key words best describing the paper. These should be chosen from the list on the journal website DHM Key words 2021 or on the Manuscript Manager website. New key words, complementary with the US National Library of Medicine NML MeSH, https://www.nlm.nih.gov/mesh/meshhome.html/ may be used but are at the discretion of the Editor. Do not use key-word terms that already appear in the title of your article.

Text format: The preferred format is Microsoft Office Word or rich text format (RTF), with 1.5 line spacing, using both upper and lower case throughout. The preferred font is Times New Roman, font size 11 or 12. Please avoid using auto formatting tools such as automatic spaces before and after paragraphs. Lines **must** be numbered **continuously** throughout the manuscript to facilitate the review process.

Section headings should conform to the current format in DHM
This is:
Section heading (for Introduction, Methods, etc)
SUBSECTION HEADING 1
Subsection heading 2

Numbering: All pages must be numbered, but no other text should appear in the header and footer space of the document. Do not use underlining. No running title is required.

English spelling will be in accordance with the Concise Oxford Dictionary, 11th edition revised (or later). Oxford: Oxford University Press; 2006.

Measurements will be in SI units (mmHg are acceptable for blood pressure measurements) and normal ranges should be included where appropriate. Authors are referred to the online BIPM brochure, International Bureau of Weights and Measures (2006), The International System of Units (SI), 8th ed, available as a pdf at https://www.bipm.org/en/publications/si-brochure/. Atmospheric and gas partial pressures and blood gas values should be presented in kPa (atmospheres absolute [abbreviated as atm abs]/bar/mmHg may be provided in parenthesis on the first occasion). The ambient pressure should always be given in absolute not gauge values unless there is a particular reason to use gauge pressure and the distinction is made clear. Water depths should be presented in metres of sea (or fresh) water (msw or mfw). Cylinder pressures may be presented as 'bar'.

Abbreviations may be used once they have been shown in parenthesis after the complete expression. For example, decompression illness (DCI) can thereafter be referred to as DCI. This applies separately to the abstract and main text. Use generally accepted abbreviations that readers are likely to be familiar with rather than neologisms of your own invention. The overuse of abbreviations is strongly discouraged.

References: References should be numbered consecutively in the order in which they are first mentioned in the text, tables or figures where they should appear as superscript numbers, either following the statement referenced,[1] or at the end of the sentence, **after the full stop**.[1,2] Do not use references in the Abstract. References appearing in tables or figures or their legends should continue the sequence of reference numbering in the main text of the article in accordance with the position of first citing the table/figure in the text. Use MEDLINE abbreviations for journal names. Journals not indexed in MEDLINE should have the journal name written in full.

The Journal reference style is based exactly on that of the International Committee of Medical Journal Editors (ICMJE) *Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals:Sample References* (updated April 2018) https://www.nlm.nih.gov/bsd/uniform_requirements.html. Examples of the formats for different types of references (journal articles, books, monographs, electronic material, etc.) are given in detail on this website. Authors MUST consult this in preparing their reference list.

An example of a journal reference in the ICMJE format is:

Wilson CM, Sayer MDJ. Transportation of divers with decompression illness on the west coast of Scotland. Diving Hyperb Med. 2011 June;41(2):64–69.

If a journal uses continuous pagination throughout a volume (as many do) then the month and issue number should be omitted and the pagination reduced. Therefore, the shortened ICMJE version used in DHM is:

Wilson CM, Sayer MDJ. Transportation of divers with decompression illness on the west coast of Scotland. Diving Hyperb Med. 2011;41:64–9.

If an article has a unique identifier for the citation (e.g., PubMed PMID, PubMed Central PMCID or DOI number) then this must be included at the end of the reference. The format and order for this is:
doi: number. PMID: number. PMCID: number. For example:

Doolette DJ, Mitchell SJ. In-water recompression. Diving Hyperb Med. 2018;48:84–95. doi: 10.28920/dhm48.2.84-95. PMID: 29888380. PMCID: PMC6156824.

An example book reference is:

Kindwall EP, Whelan HT, editors. Hyperbaric medicine practice, 3rd ed. Flagstaff (AZ): Best Publishing Company; 2008.

Examples of many other types of references are to be found on the National Library of Medicine site (see previous link).

When citing workshop/conference proceedings or technical reports, authors are requested to investigate their availability on-line, and provide an on-line source for the reference if available. The date that the reference was cited (year/month/day) from the source should be noted. For example:

Goodman MW, Workman RD. Minimal-recompression, oxygen-breathing approach to treatment of decompression sickness in divers and aviators. Research Report NEDU TR 5-65. Washington (DC): Navy Experimental Diving Unit; 1965. [cited 2019 Sep 12]. Available from: http://archive.rubicon-foundation.org/3342.

Additional notes regarding referencing in DHM are:

- If using **EndNote** to prepare the references in the document see EndNote website for advice. Once accepted, the final version of the submitted text should have all EndNote field codes removed.
- Verifying the accuracy of references against the original documents is the responsibility of authors.
- Personal communications should appear as such in the text and not be included in the reference list (e.g., Smith AN, personal communication, year).
- Abstracts from meeting proceedings should not be used as references unless absolutely essential, as these are generally not peer-reviewed material.
- Please avoid using auto-formatting functions like numbering, indentations, and spaces before and after paragraphs in compiling your reference list.

Tables must **not be** embedded in the main manuscript document. They are to be uploaded as separate Word documents (one document per table) in Manuscript Manager (use the 'other' category when asked to select a description of the document being uploaded). Name the document with the first author's name and table number as appropriate. Tables need to be labelled at the top of the page with **first** author name and the Table number.

Tables should be presented using MS Word table format with frames shown, auto-formatted to fit content. Please avoid complicated, large tables whenever possible. Very large tables (full page or more) may not be incorporated into the final article but, rather, displayed in the journal website as additional material at the Editor's discretion.

The title of the table and caption are not to be included in the table. These appear in the 'legends and captions' section at the end of the manuscript document. Legends should generally contain fewer than 40 words and should be thorough enough to be understood independently of the main text.

The table must be mentioned within the text of the article, e.g., "*Differences in rates of decompression illness were not significant (Table 1)*", etc. The approximate positions of tables and figures should also be identified in the manuscript text.

Figures (including photos, graphs, diagrams, illustrations and radiographs) must **not be** embedded in the main manuscript document. They are to be uploaded as separate electronic files in high resolution TIFF or JPEG format in Manuscript Manager. Name the document with the first author's name and figure number as appropriate. *Figures should be uploaded to Manuscript Manager in their numbered order, which results in them being compiled in the review document in correct order.*

The title of the figure and caption are not to be included in the figure. These appear in the 'legends and captions' section at the end of the manuscript document. Legends should generally contain fewer than 40 words and should be thorough enough to be understood independently of the main text. Magnification should be indicated in the captions for photomicrographs, and consideration given to the positioning of labels on diagnostic material as this can greatly influence the size of reproduction that can be achieved in the published article.

Graphs may be submitted either in colour or grey-scale, with no unnecessary shading, grid lines or box lines. Please choose the simplest graphical format that displays the data effectively. 3-D graphs are discouraged unless they are necessary to display 3-D data. Both markers and lines should be unique to facilitate easy discrimination of the data being presented. Special attention should be given to ensuring that font sizes within a diagram are sufficiently large to be legible should the diagram be sized for single-column presentation. The preferred font in diagrams and graphs is Times New Roman. Graph symbol keys should appear within the white space of the figure (not outside the axes) if possible or be included in the legend. Please ensure that axes are labelled using sentence case and the same data formatting conventions presented below.

Any graphs or histograms created in Excel should be sent within their original Excel file, including the data table(s) from which they were produced. This allows the journal office to edit figures for maximum legibility when printed. Upload the spreadsheet to Manuscript Manager with the other manuscript documents and select the designator 'other' and the option 'hide from reviewers' so that the spreadsheet is not incorporated in the review document.

Any photograph or radiograph of a patient must be de-identified. Patient details must be removed and photographs made unrecognizable. Colour photos are acceptable.

If any figures, images or tables are to be reproduced from previous publications, it is the responsibility of the author(s) to obtain the necessary permissions. This permission should be acknowledged in the figure caption using the format "*Reproduced with permission of .....*" or, if necessary, another format specified by the copyright holder granting permission.

Miscellaneous data formatting conventions: Please follow the following recommendations when presenting data in text, figures or graphs.

- Standard deviations and standard errors should be expressed as mean (SD), not mean ± SD.
- Composite units of measurement should be expressed as (for example) $g{\cdot}L^{-1}$ or $mL{\cdot}kg^{-1}{\cdot}min^{1}$, not g/L or mL/kg/min
- Please use a space between symbols like <, >, ≤, ≥. Thus (for example) > 25, not >25.
- Please use decimal points and not commas in decimals. For example: 2.5, not 2,5.
- Numbers greater than 999 should contain commas. For example: 1,000 or 25,300,000.
- Please leave a space between a number and unit of measurement. For example: 25 msw
- Please italicise *n* when used to indicate number and *P* when used to indicate P-values
- Please leave spaces in expressions like $n = 25$ or $P < 0.05$ (not n=25 or P<0.05).
- For number ranges please use an en dash without spaces. For example: 17–420. This also applies to page ranges when citing references.
- Percent signs should immediately follow a number without a space. For example: 51% not 51 %.

Other manuscript requirements and guidelines

DHM follows as much as possible the ***Recommendations for the conduct, reporting, editing and publication of scholarly work in medical journals***. International Committee of Medical Journal Editors; December 2015. Available from: http://www.icmje.org/recommendations/. Authors are strongly encouraged to read this and other documents on the ICMJE website in preparing their submission. Authors should also consult guidelines for specific types of study (e.g., the CONSORT guidelines for the reporting of randomised controlled trials); see http://www.equator-network.org/.

Trial design, analysis and presentation. Before preparing their manuscript, authors must read the summary advice on the journal website on the reporting of trial design, sample size calculation, statistical methods and results. http://www.dhmjournal.com/images/Docs/Trial-design-analysis-and-presentation.pdf.

Consent and ethical approval. Studies on human subjects must comply with the Helsinki Declaration of 1975, revised October 2013 (see https://www.dhmjournal.com/index.php/author-instructions for a copy).

Studies using animals must comply with National Health and Medical Research Council Guidelines or their equivalent in the country in which the work was conducted. It is insufficient to refer to previous publications for details of animal welfare and procedural care. The Physiological Society provides detailed advice regarding animal experimentation and its reporting in research publications and this link is provided with their kind permission: https://physoc.onlinelibrary.wiley.com/doi/full/10.1113/jphysiol.2010.192278.

A statement affirming Ethics Committee (Institutional Review Board) approval (and the approval number) should be included in the text at the beginning of the methods section. A copy of that approval should be uploaded with the submission. Similarly, a statement affirming the securing of written informed consent from subjects should be included in the methods where this was part of the methodology.

Clinical trials commenced after 2011 must have been registered at a recognised trial registry site such as the Australia and New Zealand Clinical Trials Registry http://www.anzctr.org.au/ or EudraCT in Europe https://eudract.ema.europa.eu/. Details of the registration must be provided in the accompanying MSF, and should also be mentioned in the methods section.

For individual case reports, evidence of informed patient consent to anonymous publication of their clinical details and/or images, etc. must be provided. Case series, where only limited anonymous summary data are reported do not require patient consent, but must have been assessed by an ethics committee and, if indicated, have ethics approval. Consult your local ethics committee if you are unsure.

Authorship: Authors must have contributed significantly to the study (see guideline to authorship at: https://www.dhmjournal.com/images/Docs/Guideline_to_authorship_in_DHM_journal-2015.pdf.
Inclusion of more than six authors in any one manuscript requires strong justification. Other contributors may be listed in the Acknowledgements section.

Mandatory submission form (MSF): A fully completed MSF must be signed by the first author and the corresponding author (if different) and must be uploaded with other manuscript documents in Manuscript Manager with all submissions, irrespective of type. Authors should be listed with the principal author first. Authors should be listed on the MSF in the order intended for the published paper. The form requires the full postal address, phone number and e-mail address supplied for the first author; if the corresponding author is not the first author, then full contact details for

both are required. The MSF is available for download on the DHM website.
https://www.dhmjournal.com/index.php/author-instructions

Conflict of interest form: All conflicts of interest by any author must be reported in summary in the Mandatory Submission Form. If your paper is accepted and any conflicts have been listed here, then more detailed information will be required using the ICMJE form available on the ICMJE website at: http://www.icmje.org/coi_disclosure.pdf. A form for each author for whom a potential conflict was listed must be submitted.

All potential conflicts of interest, financial or otherwise (e.g., consultancies, equity interests, patent-licensing arrangements, lack of access to data, or lack of control of the decision to publish) by any author must be declared. DHM reserves the right to seek further clarification as necessary. All conflicts or a declaration of no conflicts will appear at the end of the published article. Failure to report potential conflicts of interest prior to peer review may result in publication delays or rejection of the manuscript.

Authors should consult the WAME website http://www.wame.org/about/conflict-of-interest-in-peer-reviewed-medical if they need further clarification.

Peer review and publication process. All submitted manuscripts will be subject to open peer review usually by a member of the Editorial Board and/or external reviewers. Reviewer comments will be provided to authors with any recommendations for improvement before acceptance for publication, or if the article is rejected. DHM believes that a transparent review process is indicated in such a small specialty; reviewers are often able to identify the origin of manuscripts and, in the interests of fairness, the authors are, therefore, generally provided the names of their reviewers. The review process typically takes about eight weeks but can be longer. If additional reviews are needed, this will prolong the process. Papers are generally scheduled for publication in order of final acceptance. The Editor retains the right to delay or expedite publication in the interests of the Journal.

If the submission requires revision and resubmission before it can be accepted for publication (and the majority of papers do), then the revised files must be submitted by logging on again at http://www.manuscriptmanager.net/dhm with the same user name and password created for the original submission, then the article can be **resubmitted** by clicking the **resubmit** link NOT the new submission link. Do NOT create a new account.

Proofs of articles to be published will be sent to corresponding authors in pdf format by e-mail close to the time of publication. You will require Adobe Reader to access this, which may be downloaded from https://get.adobe.com/reader/. Authors are expected to read the proofs very carefully and inform the editorial office within the time specified of any minor corrections they require. Corrections should be listed in an e-mail sent to the journal address editorialassist@dhmjournal.com, or annotated electronically within the pdf file and returned to the same address. It is expected that the corresponding author will have obtained the approval of all authors for this final version.

English as a second language. Adequate English usage and grammar are prerequisites for acceptance of a paper. However, some editorial assistance may be provided to authors for whom English is not their native language. English language services can be accessed through the European Association of Science Editors (EASE) website http://www.ease.org.uk/. Alternatively, the journal office may be able to put you in touch with a commercial scientific ghost writer.

Copyright. Manuscripts must be offered exclusively to *Diving and Hyperbaric Medicine*, unless clearly authenticated copyright exemption accompanies the manuscript. Authors must agree to accept the standard conditions of publication. These grant DHM a non-exclusive license to publish the article in digital (electronic) form in *Diving and Hyperbaric Medicine*; also granting the right to sublicense third parties to exercise all or any of these rights. *Diving and Hyperbaric Medicine* agrees that in publishing the article(s) and exercising this non-exclusive publishing sub-license, the author(s) will always be acknowledged as the copyright owner(s) of the article.

Articles are embargoed for one year from the date of publication, after which they will be free to access on the DHM website. If authors wish their article to be free to access immediately upon publication, then a fee (determined by the publishers, EUBS and SPUMS) will be charged for its release. Authors may place their publication on their own institutional website using the 'restricted distribution', water-marked pdf provided but not elsewhere during the first year following publication. Thereafter, the non-watermarked pdf may be used ad lib.

Author fees. No fees are charged for publication in DHM. However, articles for publication in DHM are embargoed for 12 months. If immediate release is requested by authors then there is a charge for this, set from time to time by the publishers.

PDFs. Following publication, two electronic PDFs of articles will be forwarded to the corresponding author. One of these, watermarked "*restricted use*" may be placed on the author's institutional website during the one-year embargo following publication. Thereafter, the non-watermarked pdf may be used ad lib.

These *Instructions for authors* are available as a pdf file on the DHM website at:
https://www.dhmjournal.com/index.php/author-instructions

and on the web platform http://www.manuscriptmanager.net/dhm. They are also available on the EUBS and SPUMS websites.

Summary of files to be uploaded in Manuscript Manager when submitting an article

- Mandatory submission form
- Ethics approval letter where relevant, and/or signed patient consent
- Manuscript document
- Tables where relevant (each table as a separate Word document)
- Figures where relevant, uploaded in the order in which they should appear in the manuscript (each Figure as a separate high resolution TIFF or JPEG file)
- Excel spreadsheet with data and graphs if graphs have been generated in Excel.
- Submission letter; authors can use this to communicate any particular considerations or issues they wish the editor to be aware of in relation to their manuscript. The letter should state that the paper is being submitted exclusively to DHM.

Documents on DHM website: https://www.dhmjournal.com/index.php/author-instructions

The following pdf files are available on the DHM website to assist authors in preparing their submission:

Instructions for Authors (this document)
DHM Key words 2021
DHM Mandatory Submission Form 2020
Trial design analysis and presentation
English as a second language
Guideline to authorship in DHM 2015
Helsinki Declaration revised 2013
Is ethics approval needed?

DIVER EMERGENCY SERVICES PHONE NUMBERS

AUSTRALIA – DAN
1800-088200 (in Australia toll free)
+61-8-8212-9242 User pays
(outside Australia)

NEW ZEALAND – DAN Emergency Service
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ASIA, PACIFIC ISLANDS – DAN World
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EUROPE – DAN
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AFRICA – DAN
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+27-828-106010 (International call collect)

USA – DAN
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JAPAN – DAN
+81-3-3812-4999 (Japan)

ADSF
AUSTRALASIAN DIVING SAFETY FOUNDATION

Scholarships for Diving Medical Training for Doctors

The Australasian Diving Safety Foundation is proud to offer a series of annual Diving Medical Training scholarships. We are offering these scholarships to qualified medical doctors to increase their knowledge of diving medicine by participating in an approved diving medicine training programme. These scholarships are mainly available to doctors who reside in Australia. However, exceptions may be considered for regional overseas residents, especially in places frequented by Australian divers. The awarding of such a scholarship will be at the sole discretion of the ADSF. It will be based on a variety of criteria such as the location of the applicant, their working environment, financial need and the perception of where and how the training would likely be utilised to reduce diving morbidity and mortality. Each scholarship is to the value of AUD5,000.00.

There are two categories of scholarships:

1. ADSF scholarships for any approved diving medical training program such as the annual ANZHMG course at Fiona Stanley Hospital in Perth, Western Australia.
2. The Carl Edmonds Memorial Diving Medicine Scholarship specifically for training at the Royal Australian Navy Medical Officers' Underwater Medicine Course, HMAS Penguin, Sydney, Australia.

Interested persons should first enrol in the chosen course, then complete the relevant ADSF Scholarship application form available at: https://www.adsf.org.au/r/diving-medical-training-scholarships and send it by email to John Lippmann at johnl@adsf.org.au.
