Diving and Hyperbaric Medicine

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SPUMS

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EUBS

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Predicting oxygen toxicity

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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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Editorial

DCS or DCI? The difference and why it matters

There are few issues that generate as much confusion in diving medicine as the nomenclature of bubble-induced dysbaric disease. Prior to the late 1980s, the diagnosis 'decompression sickness' (DCS) was invoked for symptoms presumed to arise as a consequence of bubble formation from dissolved inert gas during or after decompression. These bubbles were known to form within tissues, and also to appear in the venous blood (presumably after forming in tissue capillaries). A second diagnosis, 'arterial gas embolism' (AGE) was invoked for symptoms presumed to arise when bubbles were introduced directly to the arterial circulation as a consequence of pulmonary barotrauma.[1]

This approach was predicated on an assumption that the underlying pathophysiology could usually be inferred from the nature and tempo of resulting symptoms. DCS was considered to exhibit a slower more progressive onset, symptoms were protean (including pain, rash, paraesthesias, subcutaneous swelling, and neurological symptoms), and the neurological manifestations were mainly attributable to spinal cord or inner ear involvement. In contrast, AGE was considered to exhibit a more precipitous onset (often immediately on surfacing), and the principal manifestation was stroke-like focal neurological impairment suggestive of cerebral involvement.

In 1989 an association between a large persistent ('patent') foramen ovale (PFO) and serious neurological DCS was independently reported by two groups,[2,3] and subsequently corroborated for neurological,[4–8] inner ear,[6,9] and cutaneous[10] DCS by multiple studies. The assumed pathophysiological role of a PFO in this setting was to allow bubbles formed from inert gas in the venous blood to avoid removal in the pulmonary circulation and to enter the arterial circulation. These bubbles could then pass to the microcirculation of vulnerable target tissues where inward diffusion of supersaturated inert gas from the surrounding tissue could cause them to grow.[11]

This emergence of 'arterialisation' of venous bubbles as an important vector of harm in some forms of DCS resulted in a challenge to the use of traditional 'DCS/AGE' terminology. It was suggested that very early onset of cerebral symptoms after diving could be explained not only by arterial bubbles introduced by pulmonary barotrauma, but also by venous bubbles crossing a PFO into the arterial circulation. Moreover, once venous bubbles had entered the arterial circulation they were then technically 'arterial gas emboli'; thus creating confusion with arterial gas emboli from pulmonary barotrauma. To many commentators, it made little sense to use diagnostic labels (DCS and AGE) that implied a particular pathophysiology when the two disorders might be difficult to tell apart, and had mechanistic processes in common.

An alternative approach derived at a UHMS workshop in 1991 was to shift from nomenclature that implied a particular pathophysiology, to a descriptive system that lumped both DCS and AGE together under the label "*decompression illness*" (DCI).[12] Using this system, terms to describe the organ system(s) involved and the progression of symptoms were applied. For example, a diver with worsening upper arm pain after a dive could be suffering 'progressive musculoskeletal DCI'; and a diver who lost consciousness immediately on surfacing but regained consciousness minutes later would be considered to be suffering 'remitting cerebral DCI'. Classifying cases in this manner made considerable sense at a clinical level, particularly given that there was an emerging consensus that manifestations of DCS and AGE that potentially overlapped did not require different approaches to recompression treatment.

This descriptive classification of bubble-induced dysbaric disease gained substantial traction in the community, though not always with a full appreciation by users of the intended nuances of its application. Indeed, it became increasingly common over time to see the terms DCS and DCI used interchangeably; for example, authors using the term DCI to specifically infer the consequences of bubble formation from dissolved gas. This highlights one of the shortcomings of the DCI terminology: it becomes confusing when discussing dysbaric disease at a theoretical or experimental level when the nature of the insult is known or there is a specific intent to discuss bubble formation either from dissolved gas or from pulmonary barotrauma.

The potential for confusion between mechanisms and manifestations of DCS and AGE as one of the principle drivers for adopting the DCI terminology deserves further discussion. It is tempting to suggest that if venous bubbles cross a PFO into the arterial blood then any resulting symptoms should be considered a manifestation of 'AGE'. However, there seems little sense in re-naming the primary pathophysiological event (DCS caused by bubble formation from inert gas) just because the bubbles have distributed elsewhere; especially using a name that commonly infers a completely different primary event (bubble formation from pulmonary barotrauma). Moreover, there are grounds for suggesting that these two processes may not be as difficult to distinguish as previously believed. Venous inert gas bubbles are small,[13] and of a similar size distribution to those used as bubble contrast during PFO testing.[14] Decades of experience in testing thousands of divers (and other patients) for PFO using bubble-contrast echocardiograpy have shown that even when strongly positive (that is, large showers of bubbles enter the arterial circulation), symptoms of any sort are

very rare. There are sporadic reports of evanescent visual or cerebral symptoms, but (to this author's knowledge) reports of the focal or multifocal cerebral infarctions that can be caused by large arterial bubbles introduced iatrogenically or by pulmonary barotrauma are lacking. One could argue that in the context of PFO testing the brain is not supersaturated with inert gas (which might cause small arterial bubbles to grow), but being such a 'fast tissue' nor is it likely to be after diving.[11] Thus, while sustained showers of small inert gas bubbles crossing a PFO after diving appeal as a plausible cause of transient visual symptoms or dysexecutive syndromes after diving, they are less likely to be the cause of dramatic stroke-like events occurring early after surfacing.

In the final edition of Bennett and Elliott it was suggested that one editorial approach to the terminology conundrum would be to utilise the traditional terminology (DCS and AGE) when referring specifically to the pathophysiology and manifestations of bubble formation from dissolved inert gas or pulmonary barotrauma respectively, and to utilise the descriptive (DCI) terminology in clinical discussions when a collective term is useful, or when discussing individual patients where there is either ambiguity about pathophysiology or no need to attempt a distinction.[1] Diving and Hyperbaric Medicine recommends a similar approach. The journal is reluctant to attempt to generate or apply hard 'rules' in relation to terminology of bubble-induced dysbaric disease, but we strongly discourage use of the term 'arterial gas emboli(ism)' to characterise venous inert gas bubbles that cross a right-to-left shunt such as a PFO. The pathophysiological consequences of bubble formation from dissolved inert gas should be regarded as decompression sickness (DCS). There is an expectation that authors are cognisant of the above issues and attempt to adopt terminology that reflects these considerations and best suits the circumstances of their manuscript.

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Decompression illness; Decompression sickness; Arterial gas embolism; Pulmonary barotrauma; Terminology; Nomenclature

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Front cover: A breath-hold diver performing a critical flicker fusion frequency test after a maximal dynamic apnea experiment described in this issue. Reproduced with permission from Dr Francisco de Asís Fernández.

Original articles

Calculated risk of pulmonary and central nervous system oxygen toxicity: a toxicity index derived from the power equation

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Key words
Diving risk; Hyperoxia; Recovery; Oxygen limits; Algorithm

Abstract
(Arieli R. Calculated risk of pulmonary and central nervous system oxygen toxicity: a toxicity index derived from the power equation. Diving and Hyperbaric Medicine. 2019 September 30;49(3):154–160. doi: 10.28920/dhm49.3.154-160. PMID: 31523789.)
Background: The risk of oxygen toxicity has become a prominent issue due to the increasingly widespread administration of hyperbaric oxygen (HBO) therapy, as well as the expansion of diving techniques to include oxygen-enriched gas mixtures and technical diving. However, current methods used to calculate the cumulative risk of oxygen toxicity during an HBO exposure i.e., the unit pulmonary toxic dose concept, and the safe boundaries for central nervous system oxygen toxicity (CNS-OT), are based on a simple linear relationship with an inspired partial pressure of oxygen (PO_2) and are not supported by recent data.
Methods: The power equation: Toxicity Index = $t^2 \times PO_2^c$, where t represents time and ^{c} represents the power term, was derived from the chemical reactions producing reactive oxygen species or reactive nitrogen species.
Results: The toxicity index was shown to have a good predictive capability using PO_2 with a power ^{c} of 6.8 for CNS-OT and 4.57 for pulmonary oxygen toxicity. The pulmonary oxygen toxicity index (PO_2 in atmospheres absolute, time in h) should not exceed 250. The CNS-OT index (PO_2 in atmospheres absolute, time in min) should not exceed 26,108 for a 1% risk.
Conclusion: The limited use of this toxicity index in the diving community, after more than a decade since its publication in the literature, establishes the need for a handy, user-friendly implementation of the power equation.

Introduction

Hyperbaric oxygen (HBO) is encountered during clinical treatment in the hyperbaric chamber and in diving. The risk of oxygen toxicity has become a prominent issue due to the increasingly widespread administration of HBO therapy, as well as the expansion of diving techniques to include oxygen-enriched gas mixtures and technical diving. But there is still no satisfactory method of calculating the cumulative risk of oxygen toxicity during an HBO exposure. The concept of the unit pulmonary toxic dose (UPTD), which is based on a modification of the rectangular hyperbola, was proposed in response to a request for oxygen exposure limits based on a very small amount of research data: a point at four atmospheres absolute (atm abs) (405.2 kPa) and the absence of known injury at an inspired partial pressure of oxygen PO_2 of 0.5 atm abs (50.6 kPa). It was merely descriptive, without any basis in physico-chemical or physiological mechanisms (Lambertsen 1990, personal communication).

In light of all this, it was clear that a different model was required to fit outcome data. The power law approach was adopted for this study. The power equation derived from the chemical reactions related to PO_2 which produce reactive oxygen species (ROS) and reactive nitrogen species (RNS) was shown to have good predictive capability.[1,2] The main difference between the power equation and the rectangular hyperbola is the high power of PO_2 in the former: 6.8 for central nervous system oxygen toxicity (CNS-OT); and 4.57 for pulmonary oxygen toxicity (P-OT). At a high PO_2, the rectangular hyperbola will lose its predictive power. Many researchers and physicians continue to use the UPTD model,[3,4] even where it can be shown not to match reality. The recommended boundaries for avoiding CNS-OT vary between different agencies and lack validation. The present report proposes a handy, user-friendly implementation of the power equation, provides corroboration for other measures of P-OT, and suggests preliminary CNS-OT limits at rest to complement those for conditions in which there is physical exertion.

THE POWER EQUATION AND OXYGEN TOXICITY

The power equation takes the form:

$$Toxicity\ Index = K = t^2 \times PO_2^c \quad (1)$$

where t represents time in hours or minutes, PO_2 is expressed in atm abs, and ^{c} represents the power term (specified above).

Data from 2,700 individual reports (2,039 closed-circuit oxygen active training dives at 1.2–1.6 atm abs (121.6–162.0 kPa) with a water temperature of 17–28°C, and 661 immersed hyperbaric exposures at 1.6–2.5 atm abs (162.0–253.2 kPa) with subjects exercising) were used to derive the power expression for CNS-OT, thus facilitating a maximum likelihood analysis.[1] The power expression for POT was derived from the reported means in resting dry hyperbaric exposures,[5–7] and therefore, as in the UPTD concept, the threshold for severity of the exposure is presented regardless of variability.

Rate of recovery was assumed to be in proportion to the severity of injury, which leads to the exponential equation (common in recovery from many injuries):

$$\text{Toxicity Index}_{tr} = \text{Toxicity Index}_{e} \times e^{-\tau \times tr} \quad (2)$$

where the subscript e represents the end of the hyperoxic exposure, tr is the recovery period, and τ is the time constant.

In principle, no threshold was incorporated in the power expression, which operates when ROS and RNS production overpowers antioxidant activity.[1] In a dry chamber saturation dive at 450 metres' sea water (msw) for 210 h, followed by 51 h at 360 msw, and with an inspired PO_2 of 0.5–0.6 atm abs (50.6–60.8 kPa),[8] part of the deterioration in lung function could be ascribed to P-OT. The calculated P-OT index was 4,433, which is very high. It is suggested that, in prolonged exposures with a relatively low PO_2, a recovery process may accompany the development of P-OT to attenuate but not entirely eliminate the toxic outcome. In CNS-OT, the threshold between the development of toxicity and recovery is between an inspired PO_2 of 1.2 and 1.3 atm abs (121.6–131.7 kPa).

PULMONARY OXYGEN TOXICITY

The derived power equation for the loss of vital capacity (VC) in our previous work was:[1]

$$\Delta VC\% = 0.0082 \times t^2 \times (PO_2)^{4.57} \quad (3)$$

where t is the time in hours and inspired PO_2 is expressed in atm abs.

Exponential recovery of pulmonary oxygen toxicity took the form:

$$\Delta VCtr\% = \Delta VCe\% \times e^{-[-0.42 + 0.384 \times (PO_2)_{ex}] \times tr} \quad (4)$$

where tr is the recovery time in hours, ΔVCtr is the value after the recovery time, ΔVCe is the value following the previous hyperbaric oxygen exposure, and $(PO_2)_{ex}$ is the previous inspired PO_2 exposure in atm abs. The rate of recovery depends on the PO_2 which caused the insult and is effective from exposure to a PO_2 > 1.1 atm abs (111.4 kPa). The value of the time constant at 1.1 atm abs may be used for PO_2 < 1.1 atm abs.

For a square exposure (at a constant inspired PO_2), to determine the expected decrement in VC, Eq. 3 applies. For a complex exposure, during which PO_2 varies and recovery periods at oxygen pressures below 0.50 atm abs, a complex calculation is required. For a number of periods (*n*) of continuous hyperoxic exposure, each for a different length of time and at a different PO_2, the calculation should take the form:

$$\Delta VC\% = 0.0082 \times [\sum_{i=1}^{n} ti \times (PO_2 i)^{2.28}]^2 \quad (5)$$

When the PO_2 changes continuously with time, Eq. 6 should be used:

$$\Delta VC\% = 0.0082 \times [\int_0^{tox} (PO_2 i)^{2.28} dt]^2 \quad (6)$$

where *tox* is the total time in hyperoxia.

When there is a recovery period in between the hyperoxic exposures, ΔVC% at the end of recovery should be calculated from Eq. 4. The time required to obtain the same ΔVC% for the next PO_2 (PO_2nx) in the hyperoxic exposure will then be derived by rearranging Eq. 3 thus:

$$t^* = [\%\Delta VC / (0.0082 \times (PO_2 nx)^{4.57})]^{0.5} \quad (7)$$

This calculated time t* should be added to the time of the coming hyperoxic period, as if the whole exposure started from this PO_2.

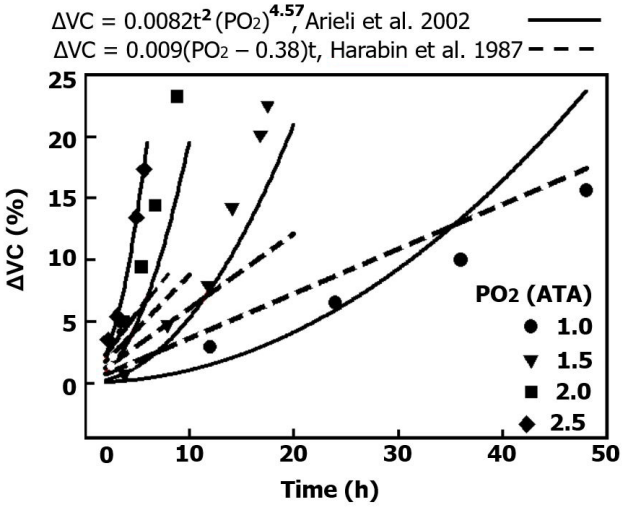
A comparison of the prediction provided by the power equation (present study) and the UPTD approach is shown in Figure 1. The adjusted reduction in VC predicted by UPTD[4] fails to follow the measured data.[5–7]

The US Navy recommended oxygen exposure limits that will result in a 2% change in VC, maximum exposure being expected to produce a 10% decrement.[3] Thus, inserting ΔVC = 2% or ΔVC = 10% into the power equation will set the PO_2 and time limits. For these two values of ΔVC, the pulmonary oxygen toxicity index $t^2 \times (PO_2)^{4.57}$ should not exceed 244 and 1,220, respectively, both at a constant pressure and for a complex exposure. This index is proposed as a replacement for the UPTD concept. With regard to the UPTD concept, a study which conducted a thorough examination of the various models concluded that "*the UPTD model should not be used except for steady exposures to PO_2 of approximately 1 ATA and for times up to 1000 min*".[9]

A recently published study[10] suggested other measures (incidence of symptoms, incidence of changes in forced vital capacity (FVC), forced expiratory volume 25-75 (FEV_{25-75}), forced expiratory volume in one second (FEV_1), or diffusing

Figure 1

Prediction by two models of the reduction in pulmonary vital capacity at four oxygen pressures as a function of time: the Naval Medical Research Institute modified pulmonary toxicity dose (broken lines), and the P-OT index (solid lines). ATA = atmospheres absolute pressure. Reproduced (with modifications) with permission from reference 1



capacity for carbon monoxide (DLCO) to replace changes in VC in the evaluation of P-OT. Because the units of the P-OT index are squared for time and the powered PO_2, this index can also accommodate other estimates. A comparison of the two methods is provided in Figure 2.

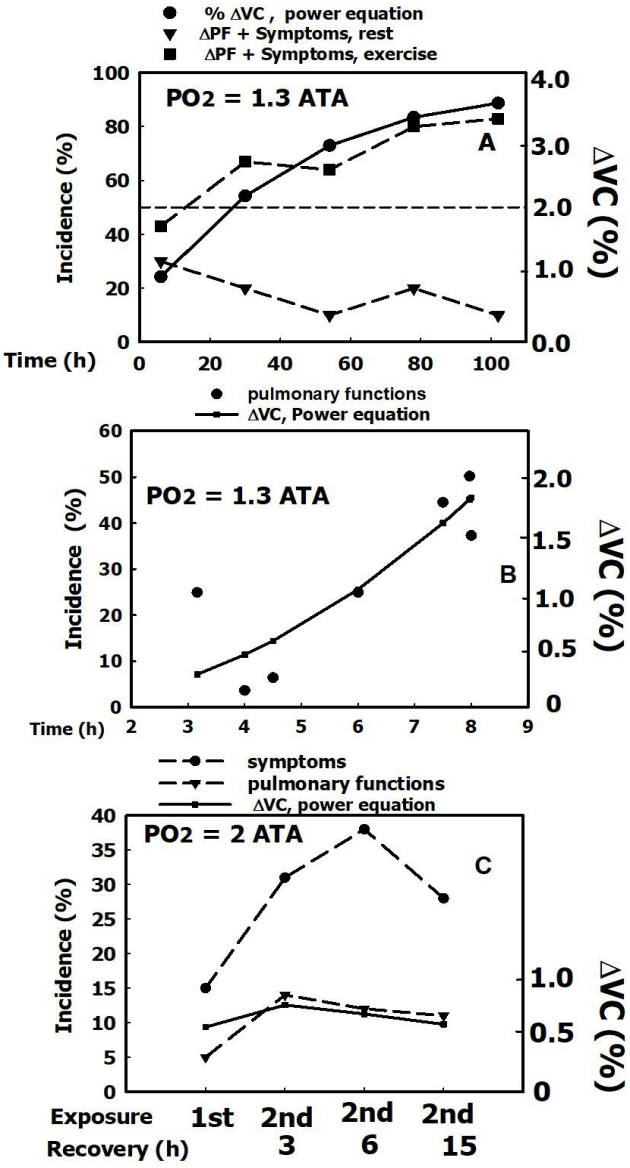
Divers made five consecutive daily dives for six hours breathing either oxygen at 1.3 atm abs or air.[11] The present author subtracted the percentage of divers who had either pulmonary symptoms or reduced volume flow after the air dives from the percentage of divers suffering from symptoms or reduced flow after the oxygen dives, taking this difference as the percentage of divers with pulmonary oxygen toxicity. The percentage of divers with P-OT after remaining at rest or performing moderate exercise during the dive is plotted against time in Figure 2A. The reduction in VC as calculated using the oxygen toxicity index, which takes into account accumulation and recovery at the end of each O_2 exposure, is also shown. It can be seen that the ΔVC calculated using the toxicity index correlates with the number of divers with P-OT during exercise; a condition in which toxicity is more prevalent. This also reinforces our approach to recovery.

In another study,[12] groups of exercising divers were exposed to 1.3–1.4 atm abs (131.7–141.8 kPa) inspired PO_2 for variable times; the incidence of P-OT is plotted in Figure 2B together with the calculated ΔVC. Agreement can be seen between the incidence of P-OT and the ΔVC calculated from the toxicity index.

In the previously mentioned study,10 subjects were exposed to 2 atm abs (202.6 kPa) O_2 in a dry chamber for 3 h, and again to the same protocol after recovery periods of either

Figure 2

Percentage of divers with P-OT symptoms (inspiratory burning, cough, chest tightness and dyspnoea), pulmonary function (PF) parameters (FVC, FEV_{25-75}, FEV_1) or their combination (symbols and dashed lines), and the calculated reduction in VC obtained using the P-OT index (solid lines). Evaluation conducted after: A) Five consecutive daily dives at rest or exercising for 6 h (PO_2 = 1.3 atm abs).[10] B) Single dives (exercise, 1.3 atm abs O_2) for different lengths of time;[11] C) A single dive (3 h, 2 atm abs O_2), and a second dive under the same conditions after a recovery period of 3, 6 or 15 h;[12] Five consecutive daily dives at rest or exercising for 6 h (PO_2 = 1.3 atm abs).[10] Note the agreement between the incidence of P-OT and the ΔVC calculated using the P-OT index. ATA = atmospheres absolute pressure



3, 6 or 15 h. The incidence of P-OT is shown together with the calculated ΔVC in Figure 2C. A good correlation is seen between the incidence of P-OT and the calculated ΔVC. The P-OT index can thus predict both ΔVC and the incidence of P-OT, which strengthens the argument for its use in determining exposure limits.

Table 1
P-OT index (K) calculated for exposures to 2 atm abs oxygen until termination due to the severity of pulmonary symptoms. Data from Widell et al[13]

Exposure	O_2 time (h)	Total time (h)	K
Continuous	5.8	6	799
25 min O_2, 5 min air breaks	8.2	9.8	1,154
20 min O_2, 20 min air breaks	6.9	13.8	412
10 min O_2, 20 min air breaks	5.1	15.4	145

In another investigation,[13] subjects were exposed to 2 atm abs oxygen either continuously or with intermittent air breathing until termination due to severe P-OT (Table 1). The P-OT index was calculated for these exposures. For continuous exposure, 25 min O_2 breathing periods with 5 min air breaks, and 20 min O_2 breathing periods with 20 min air breaks, the toxicity index was between 412 and 1,154, which is within the suggested range of 244–1,220 for a 2% and 10% ΔVC. Only for a fourth condition (10 min periods of O_2 breathing with 20 min air breaks) was a low toxicity index (145) noted. This could be related to the fact that the last protocol had the longest total exposure time of 15.4 h. It may be that mild symptoms of P-OT cannot be tolerated over such a long time.

Therefore, it is proposed that ΔVC be replaced by the P-OT index for the measurement of P-OT. Thus, to calculate the P-OT index (K), the multiplication by 0.0082 may be omitted from Eq. 3, 5 and 6, ΔVC will be replaced by K in Eq. 3, 4, 5 and 6, and Eq. 7 will be replaced by $t^* = [K/(PO_2nx)^{4.57})]^{0.5}$. In summary, it is suggested that for the most common exposures the P-OT index limit be set at 250.

CENTRAL NERVOUS SYSTEM OXYGEN TOXICITY (CNS-OT)

It is clear that in diving the risk of CNS-OT must also be taken into consideration. The various symptoms related to CNS-OT (nausea, numbness, dizziness, twitching, hearing and visual disturbances and convulsions)[1,14] were used for the calculations. These symptoms were shown to precede loss of consciousness underwater during exposure to a PO_2 of 1.5 to 1.6 atm abs (152.0–162.0 kPa).[15]

The power equation for CNS-OT was similar in form to that derived for P-OT:

$$K = t^2 \times (PO_2)^{6.8} \quad (8)$$

where K is the *CNS-OT index*, t is the duration of the hyperoxic exposure in minutes, and PO_2 is expressed in atm abs. Risk is related to the magnitude of K.

Recovery of CNS-OT risk will occur when the diver is exposed to a PO_2 below 1.3 atm abs. The exponential recovery expression is:

$$Ktr = K_e \times e^{-0.079 \times tr} \quad (9)$$

where the subscript e represents the end of the hyperoxic exposure and tr is the recovery period in min.

In a complex hyperbaric exposure comprising a number of periods of hyperoxia (in excess of 1.3 atm abs), the following two expressions (similar to those derived for P-OT) may be used for a sequence of distinct pressures and for a continuous function of PO_2 with time, respectively:

$$K = [\sum_{i=1}^{n} ti \times (PO_2i)^{3.4}]^2 \quad (10)$$

$$K = [\int_0^{tox} (PO_2i)^{3.4} dt]^2 \quad (11)$$

When there is a recovery period in-between the hyperoxic exposures, K should be calculated from Eq. 9. The time required to obtain the same K for the next PO_2 (PO_2nx) in the hyperoxic exposure will then be derived by rearranging Eq. 8 thus:

$$t^* = [K / (PO_2nx)^{6.8}]^{0.5} \quad (12)$$

This calculated time t* should be added to the time of the coming hyperoxic period, as if the whole exposure started from this PO_2.

Risk calculation

Risk calculation may be derived from the standard normal probability using the *CNS-OT index,* which is the value K derived for a specific dive profile:

$$Z = [\ln(K^{0.5}) - 9.63] / 2.02 \quad (13)$$

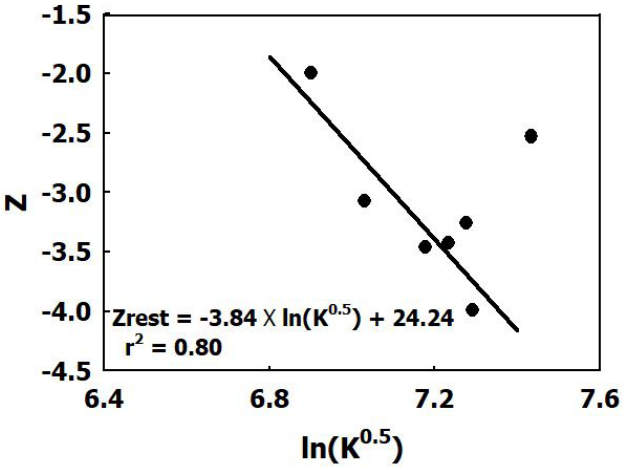
The desired risk limit may be determined by rearranging Eq. 13 thus:

$$K = [e^{2.02 \times Z + 9.63}]^2 \quad (14)$$

This enables one to find the *CNS-OT index* for the selected risk. For example, the *CNS-OT index* should not exceed 58,571 for a 2% risk, 196,811 for a 4% risk, and 432,700 for

Figure 3

The corresponding risk value Z in resting conditions, plotted as a function of the logarithm of the square root of the *CNS-OT index* (calculated using the exercise parameters); data taken from different sources (references in the text). Results of the linear regression are also shown



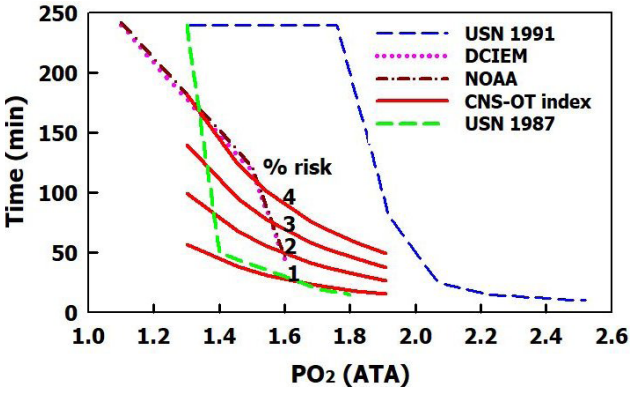
a 6% risk. The data used for the power equation were from divers exercising with an O_2 consumption of approximately 1.3 L·min^{-1}.[1,2] One must, therefore, expect a greater or lesser risk than that selected due to any alteration in metabolic rate above or below 1.3 L·min^{-1} and hypercapnia.[1] For deep diving, a low risk should be adopted.

The parameters derived for exercise were used to examine resting conditions. In US Navy Treatment Table 6 (USN TT6), calculating the toxicity index for the first three 20-min oxygen breathing periods and the two intervening 5-min recovery periods breathing air gave the values at the end of each stated period (× 10^5): 4.6 (first oxygen breathing period), 3.1 (first air break), 15.2 (second oxygen breathing period), 10.3 (second air break), and 28.7 (third oxygen breathing period). The maximum level after the third oxygen breathing period at 2.83 atm abs (286.7 kPa) corresponds to that stage in the treatment at which most of the convulsions were reported.[16] However, the *CNS-OT index* calculated for the reported incidence of 0.56% from one hyperbaric treatment facility was 7.6 times that for a calculated risk of 0.56% with exercise at 1.3 L·min^{-1}. In a similar vein, the German Navy reported a 3% incidence of CNS oxygen toxicity in their oxygen tolerance tests,[17] but the calculated *CNS-OT index* was 28 times the value for exercise with the same 3% risk. It would appear that a higher *CNS-OT index* may be tolerated in resting conditions.

For an estimation of the *CNS-OT index* at rest, data were collected from reported HBO exposures in resting conditions.[16–20] K was calculated from the exposure profiles, and based on our finding of a linear relationship between Z and ln($K^{0.5}$),[1,2] Z for the appropriate incidence is plotted against ln($K^{0.5}$) in Figure 3. Most of these data refer to seizures rather than the preceding symptoms. The equation thus derived for the value of Z (excluding one extreme point,

Figure 4

Permissible exposure to hyperoxia (PO_2/time) to avoid CNS oxygen toxicity in diving; data from different institutes. Both 1987 and 1991 US Navy recommendations are shown. The calculated percentage risk using the *CNS-OT index* is also shown



calculated for USN TT6)[16] is:

$$Zrest = -3.84 \times \ln(K^{0.5}) + 24.24 \quad (15)$$

Caution will be required when using this equation, because the parameters of the power equation were derived for exercise. Therefore, this equation can be used only as a preliminary approximation. Evidently, increased risk should be related to an increase in the index of toxicity. It now remains to solve the power equation for hyperoxic exposure at rest in the same way we did,[1] using the vast amount of individual data that has been amassed. When that is completed, we will be able to exclude from HBOT patients having a clinical condition that sensitizes them to CNS-OT, or desensitize them perhaps by means of a ketogenic diet. With the newly derived power, we should see the slope in Figure 3 change sign. The present analysis supports the general applicability of the power equation and the *CNS-OT index*.

Discussion

The PO_2/time limits calculated using the *CNS-OT index* for active diving are compared with other commonly employed limits in Figure 4. There is a vast difference between the US Navy limits in 1991[21] and those promulgated in 1987, and those of the National Oceanographic and Atmospheric Administration (NOAA) and the Defense and Civil Institute of Environmental Medicine (DCIEM),[22] with the Israeli Navy limits positioned somewhere in between those of the NOAA and the US Navy in 1991. The assumption of a linear relationship with PO_2 for the purpose of establishing the NOAA boundaries[22] evoked the comment: "*These limits were based on best judgment from extensive experience, not on the statistical analysis of quantitative data.*"[23] In a summary of the Duke University and US Navy models, the same authors concluded: "*Thus, while oxygen toxicity models are useful for illustrating principles, predictions for partial pressures of 1.6 atm or less are unreliable at best.*"[23] The

limits calculated using the *CNS-OT index* for a 1% risk are close to the US Navy's 1987 limits (Figure 4). Therefore, it is suggested that the *CNS-OT index* should not exceed 26,108.

The predictive power of the *CNS-OT index* was proved in complex exposures which had not been included in the calibration procedure.[2] It has been used for planning excursion dives in the Israeli Navy, and has been proposed for use in the Royal Netherlands Navy.[24] It has also been used in the calculation of safe submarine escape procedures in both humans and goats,[25,26] and was successfully employed in the prediction of convulsions in the resting rat.[27,28] Acclimation to hyperoxia is a factor which also requires to be taken into consideration, as shown in dives using closed-circuit oxygen apparatus.[14] Thus, experienced oxygen divers may safely adopt a higher *CNS-OT index* compared with the unacclimated diver. The proposed boundaries for any chosen percentage risk are for any symptom of CNS-OT, and it should be borne in mind that convulsions and loss of consciousness in Israeli Navy divers (3–6 msw), generally follow the appearance of several milder symptoms.[15]

Conclusions

The oxygen toxicity index is based on the suggested chemical reactions which produce ROS and RNS, and its correlation with the insult of oxygen toxicity should allow a reasonable level of predictive validity. It is proposed as a superior alternative to existing methods of calculating the safe PO_2/time boundaries for oxygen toxicity.

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Increasing prevalence of vestibulo-cochlear decompression illness in Malta – an analysis of hyperbaric treatment data from 1987–2017

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Key words
Decompression sickness; Diving; Scuba; Recompression; Symptoms

Abstract
(Azzopardi CP, Caruana J, Matity L, Muscat S, Meintjes WAJ. Increasing prevalence of vestibulo-cochlear decompression illness in Malta – an analysis of hyperbaric treatment data from 1987–2017. Diving and Hyperbaric Medicine. 2019 September 30;49(3):161–166. doi: 10.28920/dhm49.3.161-166. PMID: 31523790.)
Introduction: Scuba diving is a big part of the tourism sector in Malta, and all the cases of decompression illness (DCI) are treated within the single hyperbaric referral centre in the country.
Methods: This retrospective analysis reviews all the medical records of divers with DCI in Malta within the 30-year period between 1987 to 2017 who required recompression therapy with hyperbaric oxygen.
Results: There were 437 discrete cases of DCI managed with recompression therapy. Amongst DCI subtypes, the prevalence of musculo-skeletal DCI is decreasing, whereas that of vestibulo-cochlear DCI is increasing.
Conclusion: The increasing prevalence of vestibulo-cochlear DCI may be due to a change in diving practices in Malta.

Introduction

Malta is located in the middle of the Mediterranean Sea, with many dive sites peppered around the islands, from reefs shallower than 20 metres' sea water (msw), to wrecks as deep as 120 msw available for exploration and diving. It is well connected to the rest of the world, and with an increasing popularity of diving and ease of travel, coupled with clear water visibility and a warm temperate climate all year round, diving is an important sector of the tourism industry in Malta. There are currently 61 licensed diving schools under the remit of the licensing authority for the diving sector in Malta, the Malta Tourism Authority, and the dive schools are organised under the umbrella of the Professional Diving Schools Association. From an audit of the diving sector performed in 2015, approximately 140,000 dives by 35,000 individual divers were performed in 2015.[1] Of these 140,000 stated dives, 19 divers required recompression, giving an incidence rate of decompression illness (DCI) of 1.357 per 10,000 dives, which is close to the often-reported range of 0.41 to 3.11 per 10,000 dives incidence rate for DCI worldwide.[2,3] In an ideal scenario, an accurate denominator of total dives performed per year would be available, but this is, in most cases, never available due to logistical reasons.

The number of diving-related accidents is well documented, since there is an internal medical record registry of DCI requiring recompression with hyperbaric oxygen therapy within the single referral hyperbaric unit in Malta. This study will describe the cases requiring recompression between 1987 and 2017 within the only hyperbaric referral facility in Malta. For this geographic region, there are no similar studies published in the literature. It was the impression of one of the authors (SM) that over the 30 years of his practice of diving medicine in Malta, the prevalence of musculoskeletal decompression illness was decreasing, coupled with an apparent increase in vestibulocochlear decompression illness. We thus sought to collect and statistically analyse the dataset and see if this personal impression found support in the form of a statistically significant result.

Methods

The study was submitted for ethics review by the Health Research Ethics Committee of Stellenbosch University (ethics number: UEA-2018-7529) and approved after conforming to national and international ethics principles, codes and standards. A waiver of informed consent was granted by the ethics committee.

Figure 1
Age distribution of divers recompressed to manage DCI in Malta for the period 1987–2017 (n = 437)

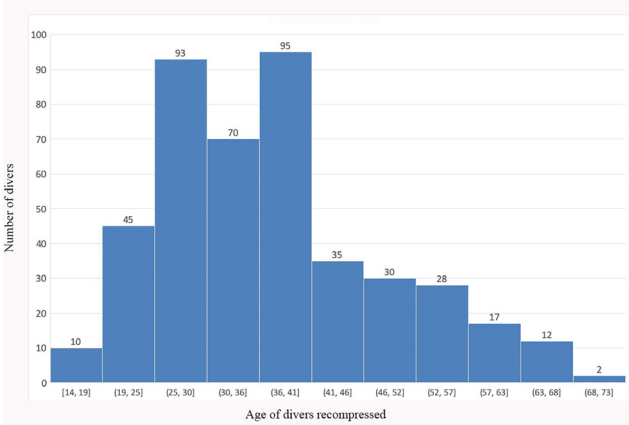


Figure 2
Choice of therapeutic table chosen in cases of divers recompressed to manage DCI in Malta for the period 1987–2017

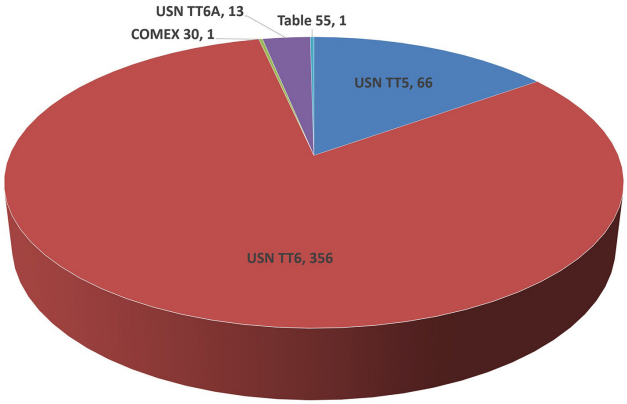


Figure 3
Sub-types of DCI in divers recompressed in Malta for the period 1987–2017. AGE = arterial gas embolism

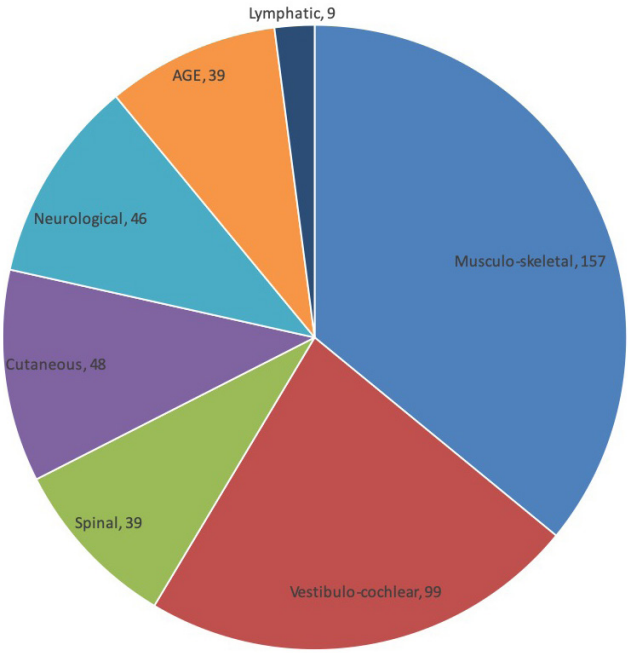
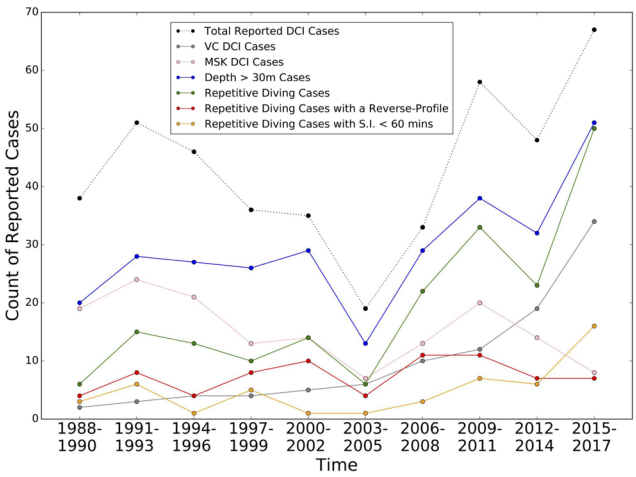


Figure 4
Trends in DCI cases 1988 to 2017. MSK = musculoskeletal. VC = vestibulocochelar



This study comprises an analysis of all the cases of DCI which were managed with recompression in the Maltese hyperbaric unit chambers between 1987 and 2017. The recompression chambers are situated within a tertiary care hospital; this was St Luke's Hospital between 1989 and 2007 and Mater Dei Hospital between 2008 and 2017. Prior to 1989, diving emergencies were treated in a Royal Navy recompression chamber manned by British military personnel present on the island until 1979, and the same chamber continued being used until 1994 by the physicians who took over from the Royal Navy (all these records have been included in the study). Scant written medical records exist prior to 1987. All records pertaining to the 1987–2017 period under analysis were captured.

STUDY POPULATION

The study sample consisted of all the divers who consulted the single referral hyperbaric centre during the 30-year study period and were managed with therapeutic recompression and hyperbaric oxygen for DCI. The term decompression illness has traditionally been used to refer to any medical illness arising as a result of lowering ambient pressure compared to a higher tissue gas pressure.[4] This includes decompression sickness (DCS) related to gas freed from solution in tissues during decompression, usually nitrogen or helium, and arterial gas embolism (AGE) caused by introduction of alveolar gas into the circulation leading to cerebral (most commonly) or coronary injury.

A patient was eligible for inclusion in the study if the written medical record file was identified as a result of a manual search of the paper medical records for all the years covering the study period, but if the consultation itself was not related

Table 1
Numbers of DCI cases, with musculoskeletal (MSK) and vestibulocochlear (VC) subtypes, for the period 1988–2017. Numbers of cases involving depth greater than 30 msw, repetitive diving, repetitive diving with a surface interval less than 60 minutes, and repetitive diving with reverse dive profiles are also shown. SI = surface interval between dives

Years	VC DCI	MSK DCI	Total cases	VC DCI fraction	MSK DCI fraction	Depth > 30 msw	Repetitive	SI < 60 min	Reverse profile
1988–1990	2	19	38	0.053	0.500	20	6	4	3
1991–1993	3	24	51	0.059	0.471	28	15	8	6
1994–1996	4	21	46	0.087	0.456	27	13	4	1
1997–1999	4	13	36	0.111	0.361	26	10	8	5
2000–2002	5	14	35	0.143	0.400	29	14	10	1
2003–2005	6	7	19	0.316	0.368	13	6	4	1
2006–2008	10	13	33	0.303	0.394	29	22	11	3
2009–2011	12	20	58	0.207	0.345	38	33	11	7
2012–2014	19	14	48	0.396	0.292	32	23	7	6
2015–2017	34	8	67	0.507	0.119	51	50	7	16

to diving medicine (e.g., a person undergoing therapeutic recompression for acute carbon monoxide poisoning or necrotizing fasciitis, or episodes of diving related barotrauma not involving the lungs), the file was excluded from the study.

VARIABLES

The following data were collected from the medical records: age, gender, DCI diagnosis and main organ system affected, the therapeutic table used, delay to treatment (beyond 60 minutes from development of first symptoms), treatment outcome, the depths of the dives performed on the day of the incident, the surface intervals between dives if multiple dives were performed, and whether repetitive (more than one dive per day) or reverse profile (shallow dive followed by a deeper dive) diving was performed.

STATISTICAL PROCEDURES

Linear regression analysis was used to assess the trend over time of musculoskeletal and vestibulocochlear DCI amongst all DCI subtypes. For the purpose of this analysis, the data were grouped in three-year bins, starting with 1988 (i.e., omitting 1987 data for the sole purpose of using uniform binning). The normal approximation to the binomial distribution was adopted to derive 1-sigma (i.e., 68%) binomial confidence intervals on the proportions of musculoskeletal DCI and vestibulocochlear DCI, and 1/variance weights were used for weighted least squares regression. An F-test was used to determine the model statistical significance, i.e., to test the null hypothesis that the gradient of the trend is zero, adopting a significance level of 0.05. Potential association of a given DCI subtype (musculoskeletal or vestibulocochlear) with dive variables (e.g., depth, repetitive diving, etc.) was analysed via a two-sided Fisher exact test, again adopting a significance level of 0.05. All quoted *P*-values are adjusted to account for multiple-testing. This was achieved via an adaptive two-stage linear step-up false discovery rate (FDR) controlling procedure.[5]

Results

There were 437 records identified for the study period. The age of the participants ranged between 14 and 71 years (Figure 1), with the mean age being 36(SD 11.64).

The gender distribution of divers with DCI was 78.5% male and 21.5% female. The distribution of choice of therapeutic table used for recompression can be seen in Figure 2, with

Figure 5
Linear regression analysis for the fraction of musculoskeletal DCI amongst DCI subtypes diagnosed in Malta for the period 1988–2017 presented in three-year bins. The confidence intervals represent the 1σ error, with the black, solid line representing the inverse variance-weighted fit. Adjusted $R^2 = 0.791$

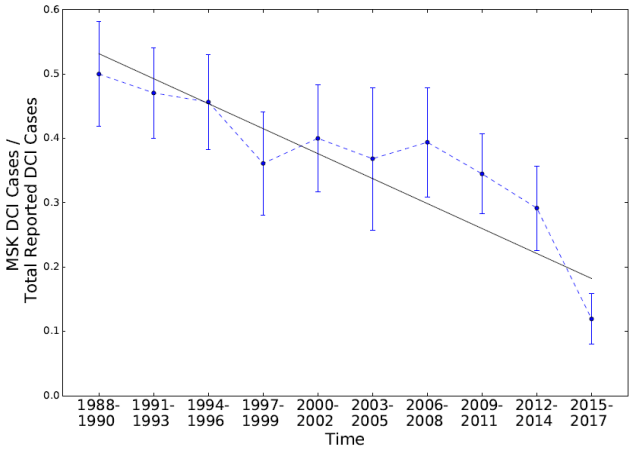


Figure 6
Linear regression analysis for the fraction of vestibulo-cochlear DCI amongst DCI subtypes diagnosed in Malta for the period 1988–2017 presented in three year-bins. The confidence intervals represent the 1σ error, with the black, solid line representing the inverse variance-weighted fit. Adjusted $R^2 = 0.836$

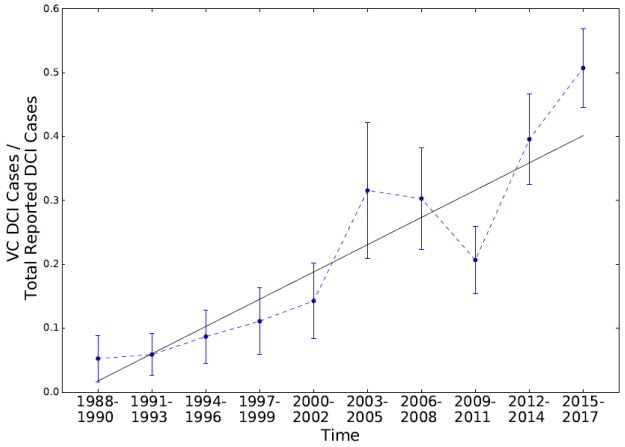
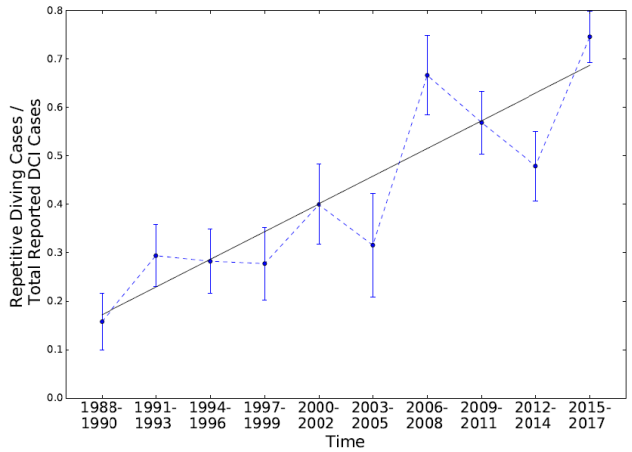


Figure 7
Linear regression analysis for the fraction of repetitive diving cases amongst total reported DCI cases diagnosed in Malta for the period 1988–2017 presented in three year-bins. The confidence intervals represent the 1σ error, with the black, solid line representing the inverse variance-weighted fit. Adjusted $R^2 = 0.832$



US Navy Treatment Table 6 being the most prevalent therapeutic table in use, while Figure 3 shows the subtypes of DCI recompressed inside the chamber during the 30-year period under investigation.

Table 1 shows the counts of musculoskeletal DCI or vestibulocochlear DCI subtypes diagnosed over the same period presented in three-year bins, together with the documented variables pertaining to each time-bin. These same data are also displayed graphically in Figure 4 for the period between 1988 and 2017. Vestibulocochlear DCI is fast becoming more commonly diagnosed amongst the various DCI subtypes.

Linear regression analysis of the fraction of musculoskeletal DCI amongst all DCI subtypes shows a statistically significant decrease over the study period ($P = 0.00037$), whereas the same analysis shows a statistically significant increase in the prevalence of vestibulocochlear DCI ($P = 0.00023$), as is shown in Figures 5 and 6 respectively. A statistically significant increasing trend ($P = 0.00023$) was also found for the fraction of cases that involved repetitive diving, as shown in Figure 7.

A two-sided Fisher exact test was employed to investigate association between a given DCI type (musculoskeletal or vestibulocochlear) and a number of dive variables, namely (1) depth (deeper than 30 msw), (2) repetitive diving, (3) reverse-profile diving (in the case of repetitive diving), and (4) a short (< 60 mins) surface interval (in the case of repetitive diving). Significantly greater proportions of dives > 30 msw (OR = 2.12, $P = 0.01614$), repetitive dives (OR = 2.74, $P = 0.00013$), and repetitive dives with reverse profiles (OR = 2.13, $P = 0.04205$) resulted in vestibulocochlear DCI. These comparisons are shown in Figures 8–10. No other associations were significant.

Discussion

Vestibulocochlear DCI typically presents with vestibular symptoms (ataxia, nausea, vomiting and vertigo), variably associated with cochlear symptoms (hearing loss and tinnitus) in two distinct situations; either during decompression from deep dives, with first symptoms developing in-water, or on surfacing from recreational open circuit compressed air dives, typically within the first 30 minutes.[6] The differential diagnosis between inner ear barotrauma and vestibulocochlear DCI (also termed inner ear DCS) is notorious in diving medicine for the difficulty it may

Figure 8
Proportions of cases with vestibulocochlear DCI who were diving less than 30 msw vs 30 msw or greater. Error bars represent 95% Wilson Score confidence intervals

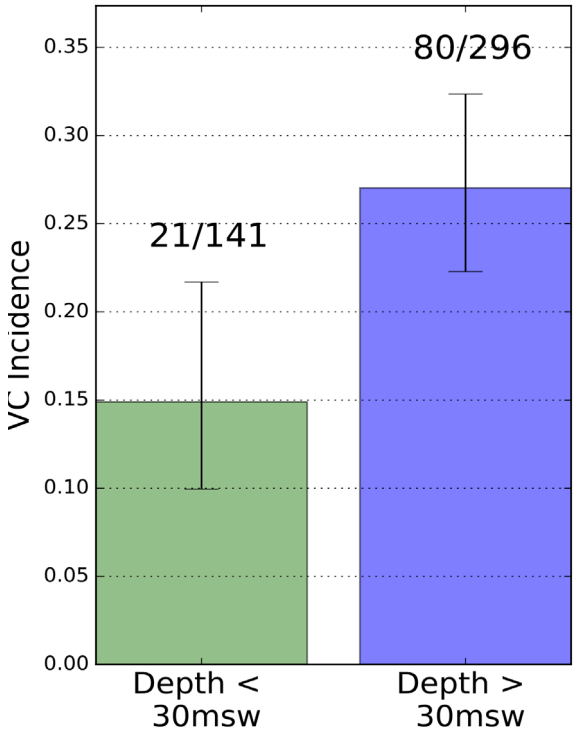


Figure 9
Proportions of cases with vestibulocochlear DCI who were performing single vs repetitive dives. Error bars represent 95% Wilson Score confidence intervals

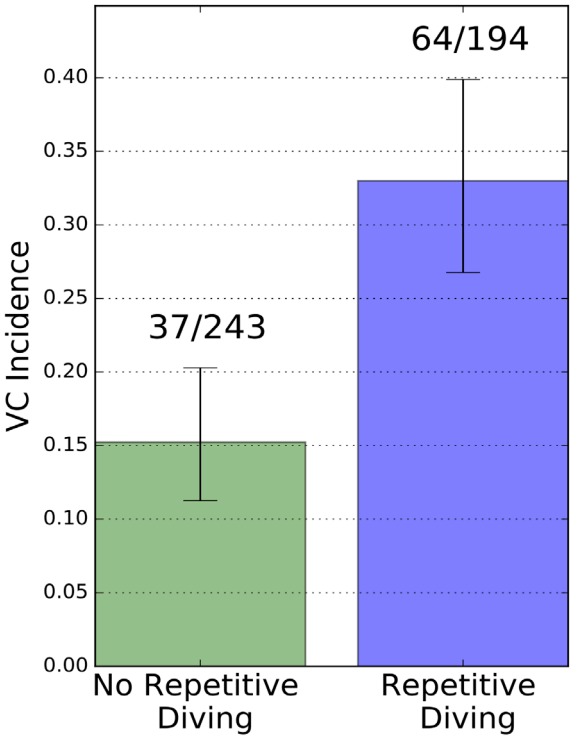
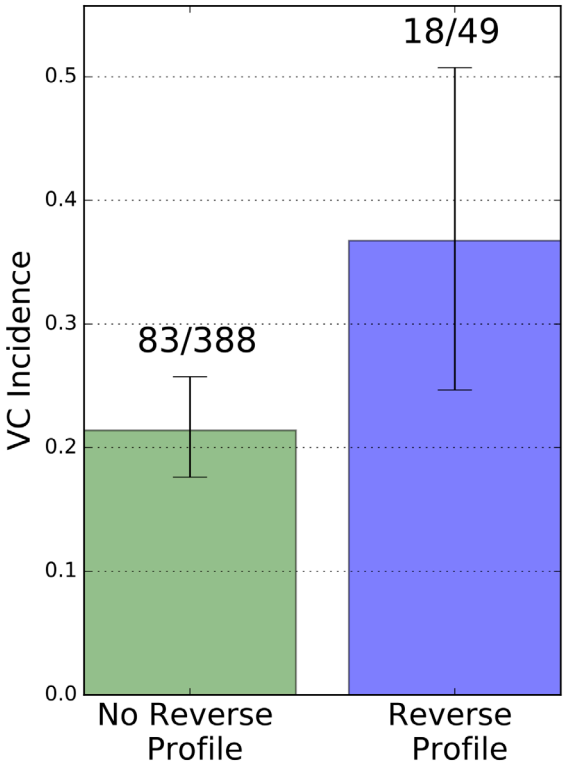


Figure 10
Proportions of cases with vestibulocochlear DCI who were diving reverse vs non-reverse profiles. Error bars represent 95% Wilson Score confidence intervals



present – inner ear barotrauma typically occurs during descent and is associated with difficulty equalizing the middle ear air space, with possible signs of middle-ear barotrauma on examination. In contrast, vestibulocochlear DCS typically presents either on ascent during decompression from deep helium dives, particularly after switches to nitrogen-containing mixes, or within 30 minutes of surfacing.[7] The difficulty also ensues at the treatment stage; the treatment of choice for vestibulo-cochlear DCS is recompression, whereas recompression is contra-indicated in cases of inner ear barotrauma.[7]

Vestibulocochlear DCI was classically described as a sub-type prevalent in mixed gas divers diving on breathing gas mixes containing helium, although it is becoming more commonly reported in recreational open circuit compressed air diving.[8–10] The pathophysiological mechanism of vestibulocochlear DCI, namely potentiation of arterialized venous gas emboli by inner ear supersaturation, especially in the setting of a right-to-left shunt such as a persistent (patent) foramen ovale, has been more recently delineated.[11,12] Our analysis shows that in Malta, vestibulocochlear DCI is associated with deep (> 30 msw) diving, repetitive diving, and reverse-profile diving.

This study provides evidence of evolving patterns of presentation in Malta over a 30 year period, influenced by the type of diving being performed. Between 1987 and 2000, the majority of DCI cases requiring recompression involved fisherman divers using SCUBA, a practice which

was outlawed in 2000 during European Union accession talks. The steady rise of vestibulocochlear DCI over the years means that it has recently become the most prevalent subtype of DCI diagnosed in divers in Malta requiring recompression, possibly due to the diving sector having moved towards repetitive and deeper recreational diving in the 20 to 40 msw range.

We acknowledge several limitations of the study. The data were extracted from the hyperbaric centre medical records and were dependent on all diving medicine physicians being diligent in their documentation; bias could be present. Data were collected from all available notes, but this does not exclude the possibly there were cases which should have been referred for therapeutic recompression, but which were managed with normobaric oxygen on-site or treated with in-water recompression by the divers themselves. Finally, it would be very desirable to have a reliable audit of the total number of dives performed per year, as this would allow a more robust analysis. However, this is rarely available due to logistical reasons. The only audit of the Maltese diving industry that is available to us pertains to a single year (2015), as described in the introduction.

Conclusions

This study was performed in order to analyse the diving population presenting to the hyperbaric chamber team, and which ended up being diagnosed as DCI and undergoing recompression therapy. We found that there is a statistically significant reduction in the fraction of musculoskeletal DCI amongst DCI subtypes diagnosed, with the same analysis showing an increasing trend for vestibulocochlear DCI. We also found a statistically significant rising trend of cases involving repetitive diving. In the case of vestibulocochlear DCI, a statistically significant association was found with deep diving, repetitive diving and reverse profile diving.

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Seizure frequency in more than 180,000 treatment sessions with hyperbaric oxygen therapy – a single centre 20-year analysis

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Key words
Hyperbaric oxygen therapy; Hyperbaric oxygen; Toxicity; Side effects; Hyperoxia; Central nervous system; Seizure

Abstract
(Costa DA, Ganilha JS, Barata PC, Guerreiro FG. Seizure frequency in more than 180,000 treatment sessions with hyperbaric oxygen therapy - a single centre 20-year analysis. Diving and Hyperbaric Medicine. 2019 September 30;49(3):167–174. doi: 10.28920/dhm49.3.167-174. PMID: 31523791.)
Introduction: Hyperbaric oxygen therapy (HBOT) involves the risk of central nervous system oxygen toxicity (CNS-OT), including seizures in patients breathing oxygen at pressures ≥ 2 atmospheres absolute. This study aimed to determine the seizure frequency and assess the clinical benefit of a 5-minute air-break (5´-AIRBK).
Methods: Twenty-year (1999–2018) retrospective analysis of all consecutive treatments with HBOT. Medical records were reviewed to determine patient demographics, comorbidities, HBOT indications, and seizure characteristics and timing. Seizure frequency was compared before and after incorporating a 5´-AIRBK in the treatment protocol. Chi-square testing was performed using SPSS (version 24.0); $P < 0.05$ was accepted as statistically significant.
Results: We evaluated 188,335 HBOT sessions (74,255 before versus 114,080 after introducing a 5´-AIRBK). A total of 43 seizures were observed: 29 before and 14 after the 5´-AIRBK introduction (3.9 versus 1.2 per 10,000 treatments; $P < 0.0001$). Seizures occurred after a median of 57 (range 15–85) minutes following compression and after a median of 21 HBOT sessions (1–126). Patients experiencing seizures were undergoing treatment for: diabetic ulcer ($n = 11$); acute traumatic peripheral ischaemia (ATPI) ($n = 6$); non-diabetic ulcer ($n = 5$); sudden sensorineural hearing loss ($n = 5$); chronic refractory osteomyelitis ($n = 5$); radionecrosis ($n = 3$); necrotising fasciitis (NF) ($n = 2$); and haemorrhagic cystitis after allogeneic bone marrow transplantation ($n = 1$). ATPI and NF had a considerably higher relative frequency of seizures compared to other indications.
Conclusions: A statistically significant lower seizure frequency was achieved with a 5´-AIRBK. Assessing and defining the appropriate patient/treatment profile can be useful to minimise the risk of CNS-OT.

Introduction

Hyperbaric oxygen therapy (HBOT) consists of breathing 100% oxygen while inside a chamber that is pressurised to greater than sea level pressure (1 atmosphere absolute – atm abs, 101.3 kPa). It is used in a number of clinical conditions as well as in professional and military training. Therapeutic HBOT usually involves pressures higher than 1.4 atm abs (141.8 kPa), frequently ranging between 2.0 (202.6 kPa) and 2.5 atm abs (253.3 kPa) for 90 to 120 minutes (min).[1–4]

Although significant adverse reactions associated with HBOT are unusual, they may influence treatment decisions for eligible patients. Higher tissue availability of oxygen promotes selective, non-hypoxic hyperoxic vasoconstriction, and redistributes peripheral blood volume in favour of hypoxic tissues (Robin-Hood effect).[4] This initial process has a protective function in that it avoids abrupt elevation of the partial pressure of oxygen (PO_2) at the cerebral level. Subsequently, in a sustained hyperbaric hyperoxic environment, there is a secondary increase in regional cerebral blood flow (rCBF). However, this biphasic response (transient vasoconstriction followed by vasodilation) is less pronounced for total pressures between 2–3 atm abs (303.9 kPa).[5,6] In "*La pression Barométrique, Recherches de Physiologie Expérimentale*" Paul Bert, and subsequently others, described the clinical manifestations of central nervous system oxygen toxicity (CNS-OT) ranging from milder and constitutional symptoms such as anxiety, nausea, vomiting, transient vision and hearing disorders to the more severe, as obnubilation or even generalised tonic-clonic seizures.[7–10] Despite the exact aetiology of these neurological alterations being not yet fully understood, CNS-OT seems to be related to several mechanisms, namely: generation of reactive oxygen species (ROS); central nitric oxide (NO) action; and eventually glutamic acid decarboxylase

Table 1
Hyperbaric oxygen therapy protocols. atm abs = atmospheres absolute pressure; O_2 = oxygen; 5´-AIRBK = 5-minute air break

Routine protocol	January 1999 – July 2008	O_2 100% 2.5 atm abs for 75 min
	August 2008 – December 2018	O_2 100% 2.5 atm abs for 75 min + 5´-AIRBK
Emergency protocol	Acute carbon monoxide poisoning	O_2 100% 2.5 atm abs for 75 min (1 session)
	Acute traumatic peripheral ischaemia	O_2 100% 2.5 atm abs for 75 min (3 sessions) then routine protocol
	Life-threatening soft-tissue infection	O_2 100% 2.8 atm abs for 110 min (3 sessions) then routine protocol
	Central retinal artery occlusion	O_2 100% 2.8 atm abs for 110 min (1 session) then routine protocol (2 sessions)

modulation in the excitatory-inhibitory process.[10]

Several studies have shown that intermittent air breaks (AIRBK) can increase tolerance of exposure to hyperoxia, especially if the interruptions were greater than 5 min.[11–13] However, it is noteworthy that after more than 50 years of research, there are no guidelines that determine the optimal relationship between 100% oxygen and AIRBK periods during therapeutic HBOT.

This study aimed to determine the the seizure frequency during HBOT, their association with baseline patient characteristics, and to assess the clinical impact of the incorporation of a 5-min AIRBK (5´-AIRBK - defined as a 5 min period in which patient was switched from breathing 100% oxygen to chamber air) in the treatment protocol.

Methods

The study was conducted in accordance with Ethics Committee regulations, and after Institutional Review Board approval.

STUDY POPULATION AND INTERVENTION

Patients were referred for treatment at the Centro de Medicina Subaquática e Hiperbárica (CMSH), Lisbon (Portugal) from departments of several hospitals nationwide, and were grouped into categories according to the indication for HBOT. Prior to HBOT, every patient underwent a tympanogram, electrocardiogram, and chest radiograph, followed by a global medical assessment to exclude conditions contraindicating HBOT.

Within each group, patients were assigned to either the routine or the emergency treatment protocol. Both protocols are described in Table 1. The main differences between routine and emergency protocols was use of several initial treatments in a shorter space of time, and occasional use of compressions to higher pressures (for certain diagnoses) in emergencies (Table 1). Indications for the emergency protocol included acute carbon monoxide (CO) poisoning, acute traumatic peripheral ischaemia, life-threatening soft-tissue infections, and central retinal artery occlusion. We excluded paediatric patients (< 6 years), gas embolism and decompression illness because of the differences in treatment tables used for those conditions. Patients with a prior history of seizures or undergoing HBOT sessions with oxygen administered by a hood (which may increase the risk of seizures due to the accumulation of carbon dioxide[14]) were also excluded. After July 2008 a single 5´-AIRBK was included into the routine protocol at the 45 min mark.

Patients were administered HBOT in a multiplace hyperbaric chamber Haux-Starmed 2200 (Haux Life Support, Karlsbad-Ittersbach, Germany), annually certified by the European Regulation for Medical Product Manufacturers.

Data from consecutive patients treated at the CMSH, from January 1999 to December 2018 were obtained from clinical records and from the medical and diving supervisor registries that included information on the HBOT protocol administered and clinical data regarding the patients' characteristics.

During the treatment CNS-OT observed by the clinical staff and HBOT technician was followed by a policy-driven response involving the supervising physician. The staff were trained to identify the signs and symptoms of CNS-OT including nausea, facial twitching, transient vision impairment, tinnitus, dizziness, temporary loss of consciousness and seizures.

COVARIATES, ENDPOINTS, AND STATISTICAL ANALYSIS

Analysed variables included patient gender, age (years), comorbidities, the primary indication for HBOT and type and timing of the seizures within an HBOT session and during the treatment course.

The primary clinical outcome was to determine the seizure frequency during HBOT in the total cohort and assess the impact of a 5´-AIRBK on the rate of seizures.

Table 2
Clinical indications for hyperbaric oxygen therapy, with number of related sessions, patients, and mean sessions per patient

Diagnosis	Sessions *n*	Patients *n*	Sessions per patient mean
Radionecrosis	77,055	1,521	51
Sudden sensorineural hearing loss	40,155	2,673	15
Diabetic foot ulcer	30,398	741	41
Non-diabetic ulcer	22,992	862	27
Chronic refractory osteomyelitis	11,745	295	40
Acute carbon monoxide poisoning	1,988	1,982	1
Acute traumatic peripheral ischaemia	1,842	102	18
Necrotising fasciitis	852	63	14
Central retinal artery occlusion	567	174	3
Compromised graft/flap	420	21	20
Others	321	103	–
Total	188,335	8,537	22

Table 3
Frequency of oxygen toxicity seizure according to the primary indication for hyperbaric oxygen therapy. *Late-onset haemorrhagic cystitis after allogeneic haematopoietic stem cell transplantation (frequency not determined by being included in a very heterogenous diagnostic subgroup)

Diagnosis (number of patients)	Frequency	Rate per 10,000	Seizure rate (%)
Radionecrosis ($n = 3$)	3 in 77,055	0.4	0.004
Sudden sensorineural hearing loss ($n = 5$)	5 in 40,155	1.2	0.012
Diabetic foot ulcer ($n = 11$)	12 in 30,398	3.9	0.039
Non-diabetic ulcer ($n = 5$)	7 in 22,992	3	0.03
Chronic refractory osteomyelitis ($n = 5$)	5 in 11,745	4.3	0.043
Acute carbon monoxide poisoning ($n = 0$)	–	–	–
Acute traumatic peripheral ischaemia ($n = 6$)	8 in 1,842	43.4	0.43
Necrotising fasciitis ($n = 2$)	2 in 852	23.5	0.23
Central retinal artery occlusion ($n = 0$)	–	–	–
Compromised graft/flap ($n = 0$)	–	–	–
Others* ($n = 1$)	–	–	–
Total	43 in 188,335	2.3	0.023

Data were analysed using Statistical Package for Social Sciences, version 24.0 (SPSS, Chicago, IL, USA). Descriptive statistics were applied (frequencies and proportions for categorical variables and mean, median and percentages for continuous variables) and the Chi-square test was performed to compare the proportion of treatments resulting in a seizure before and after the incorporation of a 5´-AIRBK. A P-value < 0.05 was considered statistically significant.

Results

All HBOT sessions administered from beginning January 1999 to the end of December 2018 were eligible to be included in the analysis. Treatments with missing or data entry errors on key study elements (657 sessions) were excluded from the report, resulting in a final sample size of 188,335 sessions (184,811 routine; 3,524 emergency) and 8,537 patients (Table 2).

Figure 1
Timing of the seizures (minutes – X axis) within a hyperbaric oxygen therapy session. Dashed line = median

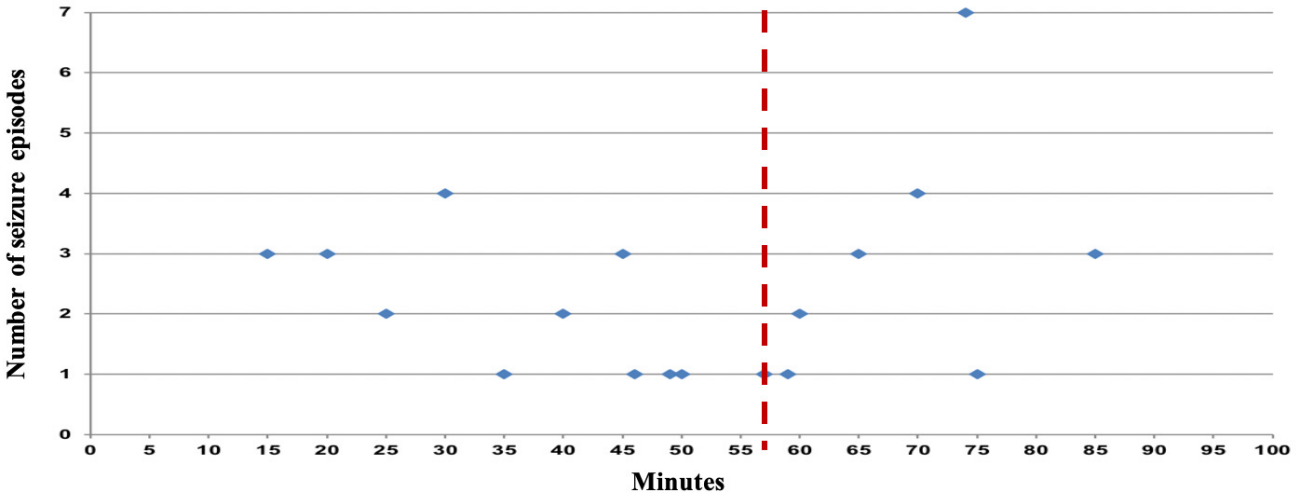
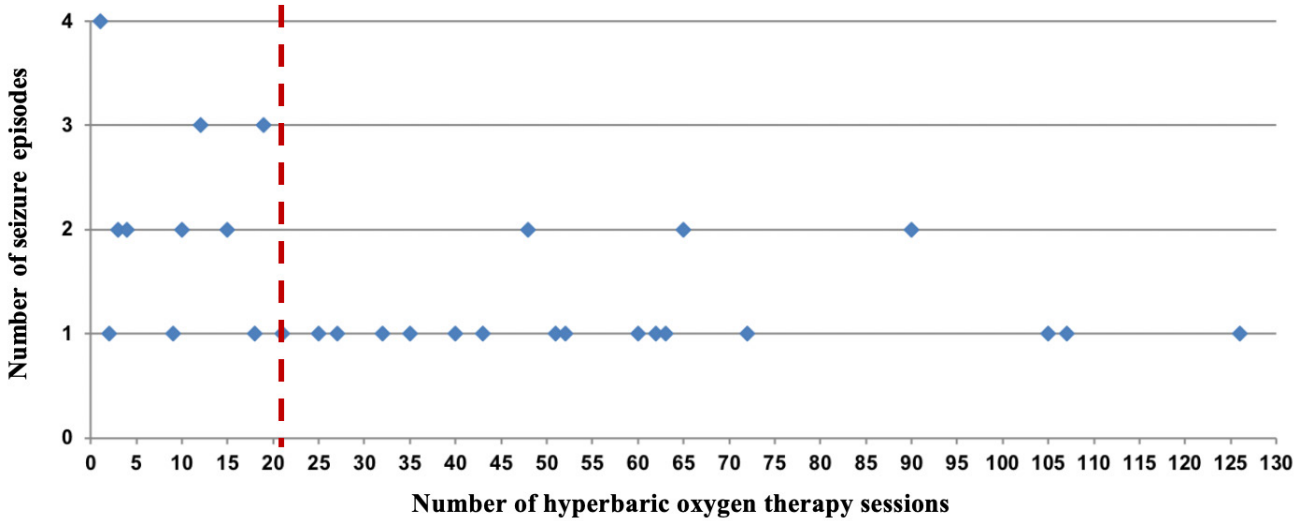


Figure 2
Timing of the seizures (session – X axis) during the hyperbaric oxygen treatment course. Dashed line = median



During the 20-year period the overall seizure rate, irrespective of the 5´-AIRBK, was 0.023% (1 in 4,379 or 2.3 per 10,000 treatment sessions) and the risk per patient was 0.45% (4.5 in 1000 patients). We documented 43 cases of seizures occurring in 38 patients (25 males; 65.8%) with a median age of 55 years (range 17–84). All seizures, except in patients treated for necrotising fasciitis and acute traumatic peripheral ischaemia occurred during routine HBOT sessions. Seizures were classified as tonic-clonic generalised (n = 41) and partial (n = 2). Seizure onset occurred after a median of 57 (15–85) min after compression (Figure 1) and after a median of 21 sessions into the treatment course (1–126) (Figure 2). There was a total of 14 episodes in 114,080 sessions (1.2 per 10,000) in patients treated with HBOT with a 5´-AIRBK, compared with 29 episodes in 74,255 sessions (3.9 per 10,000) for patients treated without a 5´-AIRBK ($P < 0.0001$).

The primary indications for HBOT in patients having a seizure were: diabetic foot ulcer (n = 11), acute traumatic peripheral ischaemia (n = 6), non-diabetic ulcer (n = 5), sudden sensorineural hearing loss (n = 5), chronic refractory osteomyelitis (n = 5), radionecrosis (n = 3), necrotising fasciitis (n = 2) and late-onset haemorrhagic cystitis after allogeneic haematopoietic stem cell transplantation (n = 1). Treatments for acute traumatic peripheral ischaemia (43.4 per 10,000 treatments) and necrotising fasciitis (23.5 per 10,000 treatments) resulted in a considerably higher frequency of seizures compared to other treatment indications (Table 3). Eight patients (2 chronic refractory osteomyelitis, 2 necrotising fasciitis, 1 diabetic foot ulcer, 1 sudden sensorineural hearing loss, 1 radionecrosis, and 1 with late-onset haemorrhagic cystitis after allogeneic haematopoietic stem cell transplantation) developed the convulsive episode in the first five sessions of HBOT.

Table 4
Frequency of oxygen toxicity seizures reported by previous studies

Study	Frequency	Rate per 10,000	Seizure rate (%)	Tx pressure atm abs
Hart 1987[15]	1 in 12,253	0.8	0.008	2–3 atm abs
Davis 1989[16]	1 in 10,552	0.95	0.009	2.4 atm abs
Welslau 1996[17]	1 in 6,704	1.5	0.015	2.4–2.8 atm abs
Plafki 2000[18]	1 in 2,844	3.5	0.035	2.4–2.5 atm abs
Hampson 2003[14]	1 in 3,388	3	0.029	2–2.8 atm abs
Yildiz 2004[19]	1 in 40,339	0.25	0.002	2–2.8 atm abs
Banham 2011[20]	1 in 1,651	6	0.061	1.9–4 atm abs
Heyboer 2014[21]	1 in 2,121	5	0.047	2–2.8 atm abs
Hadanny 2016[22]	1 in 8,945	1.1	0.011	1.5–2.8 atm abs
Jokinen-Gordon 2017[23]	1 in 5,730	1.7	0.017	2–2.5 atm abs
Sherlock 2018[24]	1 in 3,718	2.7	0.027	2.4 atm abs
Alpuim Costa 2019	1 in 4,379	2.3	0.023	2.5–2.8 atm abs

Another four patients (2 non-diabetic ulcer, 1 diabetic foot ulcer, and 1 with acute traumatic peripheral ischaemia) had a recurrence of seizures. More than half of the patients experiencing seizures (n = 21; 55%) did not complete the treatment course as a result. Among patients suffering a seizure recorded comorbidities were: diabetes mellitus (n = 15), arterial hypertension (n = 15), high intensity trauma (n = 8, 1 head trauma), heavy smoker (n = 6), dyslipidaemia (n = 6), chronic renal disease (n = 5), chronic heart failure (n = 3), chronic obstructive pulmonary disease (n = 3), cerebrovascular disease (n = 2), autoimmune disease (n = 2), active metastatic disease (n = 2), drepanocytosis (n = 1), deep venous thrombosis (n = 1); medicated regularly with analgesics (n = 10, 1 including opioids), antidepressants (n = 4) and recent high-dose intensity chemotherapy (n = 1).

Discussion

In this 20-year analysis of more than 180,000 HBOT sessions at CMSH, the overall seizure rate was less than 0.03% and introduction of the 5´-AIRBK was associated with a significant decrease in seizure frequency.

The results of this study are consistent with prior studies confirming the rarity of this event. However, in the past 15–20 years, there seems to have an increase in frequency to approximately one case in 2,000–5,000 treatment sessions. This may be related to patient selection (with more comorbidities) and modifications in HBOT protocols. Overall, there are considerable variations between the different studies reporting the seizure frequency (Table 4).[14–24] It is difficult to compare the different series that have used various hyperbaric protocols (PO_2 pressures, AIRBK, duration of exposures and number of HBOT sessions), varied techniques for oxygen delivery (hood, mask, monoplace), changeable HBOT chamber settings (CO_2 removal, equipment resistance), and variable indications and patient status (in respect of comorbidities, medications, etc.). Every one of these factors could contribute to the considerable variation in reported seizure rates.

Because of the differences in treatment tables among some group of patients, we excluded paediatric age (< 6 years), gas embolism and decompression illness to obtain reasonable treatment protocol homogeneity in our sample. A lower seizure frequency was associated with the incorporation of a 5´-AIRBK in the treatment protocol, validating previous findings that the risk of CNS-OT occurrence is often mitigated by interspersing short periods of air-breathing between 100% oxygen periods at increased pressure. The major problem is to define the limit of duration of exposure to HBOT, as there are no identifiable biomarkers that indicate the transition from the beneficial effect to the toxicity.

In this study, patients who had seizures (43 seizures in 38 patients), the majority had their convulsive episode after the first half hour of treatment (Figure 1). This fact may reflect the continued action of several factors, including an imbalance of the vaso-modulation and antioxidant defence processes.

In prolonged HBOT protocols for chronic disorders, the repeated exposure to oxygen could increase susceptibility to hyperoxic seizure. In experimental studies with mice exposed to 4 atm abs, latency to seizure shortened and severity increased after prolonged intermittent therapy. It was found that for exposures at sub-convulsive minor pressures (2 atm abs) for 2 hours, the sensitivity for

subsequent exposures to higher pressures (4 atm abs–405.2 kPa) increased significantly. This was present even after 5 sessions and persisted for at least 10 days (possibly related to NO and increased NO synthetase function).[25,26]

In our series, seizure frequency increased longitudinally throughout the treatment course. However, eight patients developed the convulsive episode in the first five sessions of HBOT (four in the first treatment session). Another four patients experienced more than one seizure episode (all before the 5´-AIRBK was introduced and even after interruption of treatment for more than one month), including one patient with three non-consecutive episodes (middle-aged, a heavy smoker, non-diabetic ulcer with arterial hypertension, dyslipidaemia, hyperuricaemia, and chronic pancreatitis). This may indicate greater individual susceptibility and or even modifications acquired in the previously mentioned mechanisms. In our centre, we generally recommend interruptions of one month after 40 or more consecutive sessions to diminish the pulmonary and CNS-OT risk. In general, the number of treatment-sessions administered to patients with seizure episodes was shorter than those without (comparing with our historical controls and protocols), indicating that when a seizure occurs, a treatment course is more likely to be ended early.

HBOT-induced seizures are accepted to be generalised, although several studies suggested specific susceptible foci for the initiation of the epileptic activity. The local sensitivity during HBOT may be related to regional variations between different brain areas with respect to rCBF, amino acids and ammonia levels, lipid peroxidation, and antioxidant enzymes distribution[6,27–32] We documented two episodes of partial seizures, possibly reflecting early abnormal changes in cortical electrical activity, that completely resolved with reduction of the inspired PO_2. Notably, none of the patients with seizures had a history of epilepsy or another neurological disease.

Environmental and personal factors may modify the sensitivity to CNS-OT, thus shortening the duration of the latent period, and lowering the threshold pressure for the development of seizures. It has been observed that age could increase susceptibility to CNS-OT (higher sensitivity to ROS and lower level of the neurotransmitter GABA) and that gender might be relevant.[33–35] In our series of seizing patients, the median age was 55 years, and the majority were male. Prior research demonstrates gender differences in healthcare utilisation behaviours; women are more likely to use preventive services and to seek care early in the disease process.[36,37] Thus, female patients may experience fewer severe comorbid conditions and may be more likely to adhere to other prescribed treatments, reducing the likelihood of treatment complications.[23]

In addition to gender and age, individual day-to-day variation, circadian rhythm, physical activity, diet, alcohol dependence, narcotic withdrawal, various drugs (opioids, analgesics, antidepressants, antibiotics, etc.), fever, chronic obstructive pulmonary disease, heart failure, acute ischaemic events and trauma may contribute to wide-ranging physiological variability in the sensitivity to CNS-OT.[9,19,23,24,38,39] The patients reported in this series suffered from a diversity of comorbidities, some of which have previously been associated with seizure risk, and some which have a plausible basis for being considered risk factors. However, our data do not allow any conclusions to be drawn on this issue.

It is noteworthy that the seizure frequency was significantly higher in patients with acute traumatic peripheral ischaemia (43.4 per 10,000) and necrotising fasciitis (23.5 per 10,000) (Table 3) even though treatment of these diagnoses took place over fewer treatment sessions per patient (Table 2). The reasons for this increased risk, despite the shorter duration of treatment are uncertain and may be related to several factors, namely: higher pressure and duration of oxygen exposure in the first three treatment sessions for necrotising fasciitis (the episodes occurred in the inaugural session of HBOT), less time for patient education concerning the potential risk factors, acute oxidative stress, CO_2 retention, fever, high intensity trauma and some drugs (opioids and antibiotics).

The current analysis is limited by several factors, including its retrospective nature, the single institution source of data, the exclusion of patients < 6 years age and with gas embolism or decompression illness, and the diversity of the population included in the 20-year period of the study. Even though the authors believe that the current findings represent an accurate depiction of seizure occurrence associated with HBOT, including critical care patients underrepresented in other studies, our medical and supervisor records must be improved.

Conclusions

In this cohort of patient-treatments (the largest reported to date), the overall seizure rate was similar to previous studies confirming the rarity of this event. Acute traumatic peripheral ischaemia and necrotising fasciitis patients exhibited a higher rate of events compared to other indications treated. The incorporation of a 5´-AIRBK was associated with a significantly lower seizure frequency. Assessing and defining the appropriate patient/treatment profile can be useful to minimise the risk of CNS-OT. We believe that a meta-analysis may provide helpful further information.

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Only minor stem cell mobilization in head and neck irradiated patients treated with hyperbaric oxygen

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Key words
Head and neck cancer; Hyperbaric oxygen; Osteoradionecrosis; Platelets; Soft-tissue radionecrosis; Stem cells

Abstract
(Forner L, Berkowicz A, Dickmeiss E, Hyldegaard O, Jansen EC, Fischer-Nielsen A. Only minor stem cell mobilization in head and neck irradiated patients treated with hyperbaric oxygen. Diving and Hyperbaric Medicine. 2019 September 30;49(3):175–185. doi: 10.28920/dhm49.3.175-185. PMID: 31523792.)
Introduction: Hyperbaric oxygen, (HBO) is used to treat several conditions including late radiation tissue injury. Previous studies have suggested that HBO mobilizes bone marrow derived stem/progenitor cells (SPC) to the peripheral blood, however possible cumulative effects were highly variable.
Methods: We have investigated a possible HBO-induced mobilization of SPCs by determining CD34+CD45dim cell numbers, as well as SPCs in general. The latter were characterized by high aldehyde dehydrogenase (ALDH) activity by use of the Aldefluor® assay. We included ten patients admitted for HBO treatment of radiation tissue injury. Six patients completed the 29–30 HBO treatment exposures. We also investigated possible HBO-induced effects on platelet activation as measured by flow cytometry and functional analyses.
Results: We found a weak and insignificant tendency toward mobilization of CD34+CD45dim cells after a single HBO exposure versus before. Additionally, we found an additive effect of 15 HBO exposures on the increase in CD34+CD45dim cells relative to the pre-1st-HBO values. These changes were significantly more than zero but less than a doubling. We could not demonstrate a significant effect of HBO on the content of Aldefluor® positive SPCs in peripheral blood. There was no significant effect on platelet activation overall. However, in patients with increased expression of activation markers at baseline, we found a decrease after one exposure although this was not reflected in functional tests.
Conclusion: We found a minor statistically significant mobilizing effect of HBO treatment on the bone marrow derived stem/progenitor cell content in peripheral blood after 15 treatments (n = 10 patients), but no effect after 30 treatments (n = 6 patients). However, because of the low number of patients we cannot confidentially prove or disprove the null hypothesis. The possibility that HBO treatment reduces the number of activated platelets could not be demonstrated nor excluded.

Introduction

Hyperbaric oxygen (HBO) is used for the treatment of a variety of conditions including late radiation tissue injury. HBO treatment has been shown to increase the number of small blood vessels in irradiated tissue. This results in increased tissue oxygen levels and improved white cell and fibroblast function, which further enhances wound healing.[1–3]

In addition, previous studies have suggested that HBO treatment induces mobilization of bone-marrow-derived stem/progenitor cells (SPCs) through, e.g., HBO-mediated oxidative stress at sites of neovascularization.[3–5] Bone marrow derived SPCs encompass a variety of progenitor cells including hematopoietic stem cells (HSCs), mesenchymal stromal cells (MSCs), and endothelial progenitor cells (EPCs).[6] Potentially, mobilization of these cells could facilitate regeneration of radiation injured tissue by EPC-induced vasculogenesis[7,8] and/or the anti-inflammatory and anti-fibrosis activity of MSCs[9] after homing of these cells to ischaemic areas. However, although three clinical studies have reported more than a doubling of circulating SPCs after one HBO exposure, the possible cumulative effect after 20 exposures has varied considerably between studies from none to more than a 20-fold increase in circulating SPCs.[4,10,11]

Determination of the mentioned cell populations can be performed by analysis of specific surface markers

characterizing each population. In addition, SPCs can collectively, regardless of the specific type, be characterized by their high activity of the cytosolic enzyme aldehyde dehydrogenase (ALDH). The SPCs therefore can be labelled by a cell-permeable fluorescent substrate (e.g., Aldefluor®) which is converted in the cytoplasm by ALDH to a charged molecule unable to leave the cell, and therefore accumulating in cells with high ALDH activity.[6]

With respect to inflammation, platelets secrete a variety of peptides and proteins in their activated state and influence the attraction of leukocytes to the endothelium.[12,13] Regarding a possible HBO-induced anti-inflammatory effect, Shaw et al., demonstrated an HBO-mediated up-regulation of relevant proteins from platelets.[14] Additionally, some studies have shown altered aggregation or numbers of platelets after HBO[15–17] while others have shown no such impact of HBO.[17,18]

In the present study, we investigated whether HBO treatment given to a group of patients with radiation induced injuries brought about a rise in peripheral blood of Aldefluor®-positive cells, representing a general SPC marker, and/or of CD34+CD45dim cells as a certain marker of HSCs and a reported marker of the much-debated EPC.[19] Moreover, we investigated whether HBO treatment induced changes in platelet activation using both flow cytometry and functional tests.

Methods

The study had an open prospective design. The study was approved by The Regional Scientific Ethics Committee of The Capital Region of Denmark and the Danish Data Protection Agency (Ethics Committee Approval Number was H-1-2010-093). Patient consent was obtained before inclusion.

PATIENTS

Ten patients received radiotherapy according to the Danish national guidelines (available from: https://www.dahanca.dk) to total doses to the tumor area of 66–68 Gy, and prophylactic nodal irradiation to a total dose of 46–50 Gy. Radiotherapy was given in 2 Gy fractions with 5 or 6 fractions per week. Each participant was referred to the hyperbaric facility because of osteoradionecrosis (ORN) or late radiation tissue injury (LRTI), including prophylactic treatment before tooth extraction. All patients with a diagnosis of mandibular/maxillary osteoradionecrosis or late radiation tissue injury were considered eligible.

Table 1 provides basic demographic information, details of the cancer diagnosis, and number of hyperbaric treatments. Table 2 provides information about patient comorbidities and medication. The exclusion criteria were: age < 18, uncontrolled hypertension, epilepsy, lack of ability to equalize pressure in the middle ear without the need to insert a drain, unmanageable claustrophobia, presence of or suspicion of pneumothorax, thoracic surgery within the last month, haemoglobin < 6 mmol·mL^{-1} (9.67 g·dL^{-1}).

HYPERBARIC OXYGEN TREATMENT

The patients were placed in a multi-place pressure chamber breathing 100% oxygen from a hood (Amron Vista, California, USA). The treatment consisted of pressurization over 5 minutes to a pressure of 243 kPa (2.4 ATA). The pressure was maintained for 90 minutes (no air breaks) followed by decompression over 5 minutes. The patients were subjected to one daily exposure five days a week for six weeks for a total number of 29–30 exposures.

BLOOD SAMPLES

Six mL of ethylenediaminetetraacetic acid (EDTA) stabilized blood was obtained before and after exposures 1, 15 and 29 or 30 to determine the absolute concentration of CD34+CD45dim cells in whole blood. Before and after exposure numbers 1 and 29 or 30, an additional 12 mL of EDTA stabilized blood was obtained for isolation of the mononuclear cell (MNC) fraction and determination of the Aldefluor® positive and CD34+CD45dim cells relative to the MNC population.

For platelet activation analyses, 3.5 mL of citrate stabilized blood and 4 mL of heparin stabilized blood was obtained before and after exposures 1 and 29 or 30.

LABORATORY METHODS

Haematological parameters

Blood cell counts, i.e. haematocrit, total white blood cells, granulocytes, monocytes and platelets were determined using a Sysmex® XE-2100D analyser (Sysmex, Kobe, Japan) according to the manufacturer's instructions.

Stem cell determination

CD34+CD45dim cell numbers were determined both by use of a single-platform on whole blood and by determining values relative to lymphocytes using MNCs obtained by lymphoprep density separation. Aldefluor® positive cells were determined only relative to MNCs. All flow cytometric measurements were done in duplicate.

For MNC separation, EDTA anticoagulated blood diluted 1:1 with RPMI 1640 (Sigma-Aldrich, Missouri) was centrifuged through Lymphoprep™ (STEMCELL Technologies, Inc., UK) 800 g for 20 min according to the manufacturer's instructions.

Aldefluor® staining with immunophenotyping of the MNC suspensions was performed using Aldefluor® staining reagents (Aldagen Inc., Durham NC, USA) and the

Table 1
Patient characteristics including demographic information, details of the cancer diagnosis, and number of hyperbaric treatments. Exp = HBO exposures; F = female; LRTI = late radiation tissue injury; M = male; ORN = osteoradionecrosis

No.	Gender /age	HBO indication	Cancer year	Localization	Exp.	Duration (days)
1	M/76	Tooth extraction	1983	Larynx	30	49
2	M/63	ORN	2008	Lingual base	29	44
3	M/63	LRTI	2010	Retromolar trigonum	24	41
4	M/47	Tooth extraction	2002	Parotid gland	30	42
5	F/81	Tooth extraction	2005	Hodgkins lymphoma	30	54
6	M/51	ORN	2011	Tonsil	30	42
7	M/63	ORN	2009	Cheek mucosa	30	42
8	F/59	ORN	2005	No information	22	42
9	F/57	LRTI	2005	Oral cavity	29	60
10	M/72	ORN	2008	Tonsil	27	43

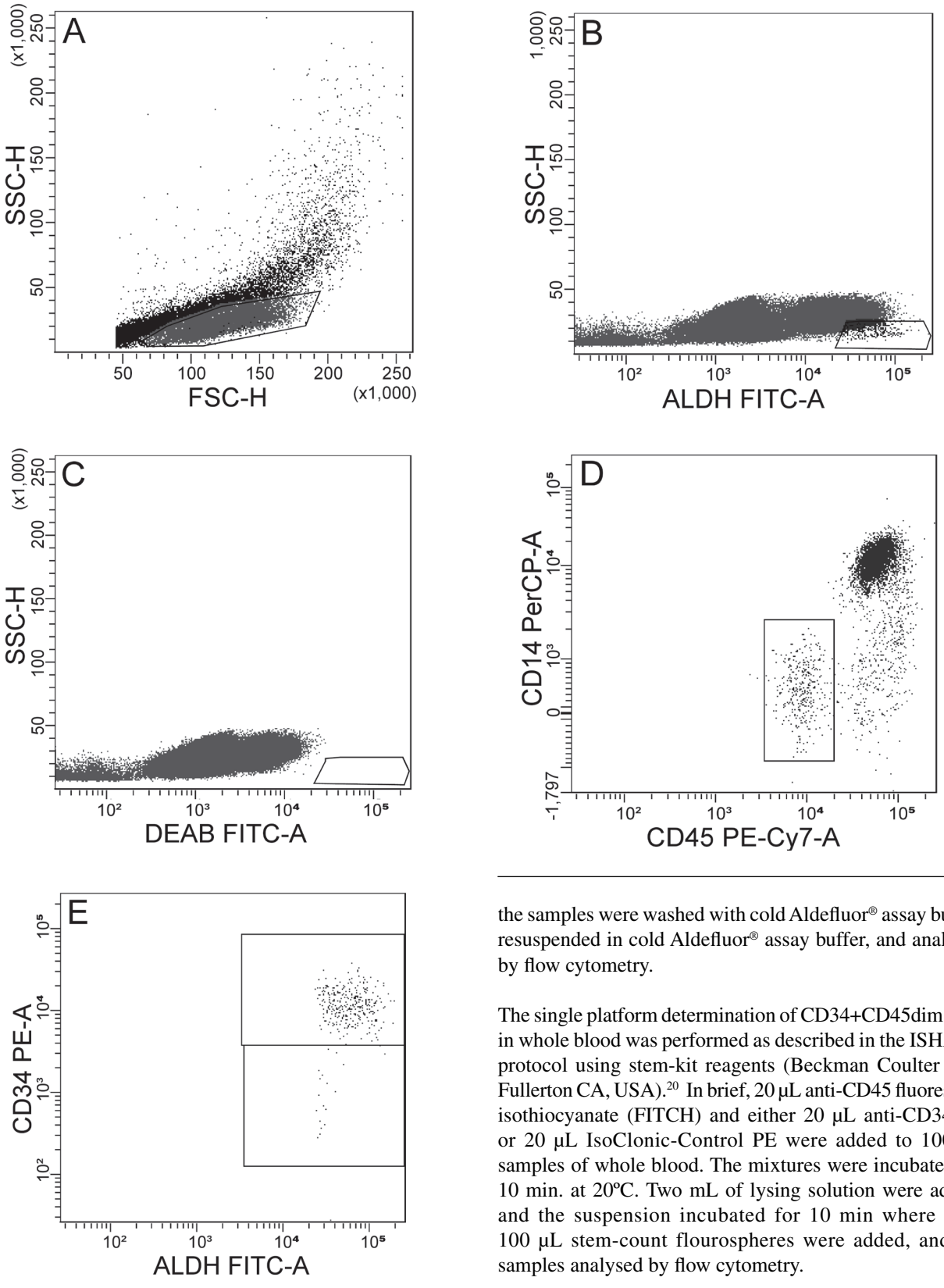
Table 2
Patient comorbidities, smoking and medications

No.	Smoking	Comorbidity	Medication
1	No	Heart disease	Salicylic acid, isoptine retard, simvastatine, venlafaxine, eltroxine
2	Yes	None	None
3	Yes	Cerebral embolism	Morphine, amlodipine, centyl with potassium chloride, plavix, paracetamol, tradolan, simvastatin
4	No	None	None
5	No	Heart disease	Digoxin, salicylic acid, centyl with potassium chloride, furosime with potassium, pantoloc
6	No	None	None
7	No	None	Dolol, paracetamol
8	Yes	Hypertension	Atenolol, corodil, halcion
9	Yes	Hypertension	Paracetamol, endofen, calepracan, codeine, amlodipine, femar, calcium
10	No	None	Paracetamol, ibuprofen

following antibodies from BD Biosciences (San Jose CA, USA): phycoerythrin (PE) labelled anti-CD34, IsoClonic-Control-PE, peridinin chlorophyll protein (PerCP) labelled anti-CD14, and PECyanin7 (PECy7) labelled anti-CD45. Staining was performed according to the manufacturer's protocol. In brief, 1.5 x 10^6 mononuclear cells were resuspended in 1.5 mL Aldefluor® assay buffer. Five µL of activated Aldefluor® reagent were added, and 0.5 mL of the suspension was transferred to each of the two control tubes containing 5 µL N,N-diethylaminobenzaldehyde (DEAB) aldehyde dehydrogenase blocking reagent. The tubes were incubated at 37ºC for 30 min and centrifuged at 300 x g for 5 min, and the cell pellets were resuspended in 55 µL cold Aldefluor® assay buffer and incubated at 4ºC for 30 min. Additionally, 20 µL anti-CD34 PE were added to the first two tubes, 20 µL IsoClonic-Control PE to the third tube, and 5 µL anti-CD45 PECy7 and 5 µL anti-CD14 PerCP were added to all three tubes before incubation. After incubation

Figure 1

Dot plots of gating strategies used in the analysis of Aldefluor® stained MNCs. MNCs were gated (Figure 1A). Next, the Aldefluor® positive cells were gated (Figure 1B). As a specific control for ALDH activity, a blocking agent (DEAB) was added (Figure 1C). The Aldefluor® positive cells were gated to separate them from the Aldefluor® CD14 positive monocytes (Figure 1D). The gated cells were analysed in Figure 1E to enumerate the CD34 positive cells and the CD34 negative cells, respectively, among the Aldefluor® positive cells



the samples were washed with cold Aldefluor® assay buffer, resuspended in cold Aldefluor® assay buffer, and analysed by flow cytometry.

The single platform determination of CD34+CD45dim cells in whole blood was performed as described in the ISHAGE protocol using stem-kit reagents (Beckman Coulter Inc., Fullerton CA, USA).[20] In brief, 20 µL anti-CD45 fluorescein isothiocyanate (FITCH) and either 20 µL anti-CD34 PE or 20 µL IsoClonic-Control PE were added to 100 µL samples of whole blood. The mixtures were incubated for 10 min. at 20ºC. Two mL of lysing solution were added, and the suspension incubated for 10 min where after 100 µL stem-count flourospheres were added, and the samples analysed by flow cytometry.

Flow cytometry

Analyses of the MNC suspensions were performed on a BD FACS Canto flow cytometer (BD Biosciences, San Jose CA, USA). The gating strategy for the enumeration of the aldeflour positive stem/progenitor cells is shown in Figure 1.

The gating strategy for CD34+CD45dim cells followed the guidelines from the ISHAGE protocol either as a single platform analysis for the whole blood method or a double platform analysis for the lymphoprep isolated MNCs. For both methods, we used a fluorescence minus one (FMO) gating strategy with isotype controls instead of unmarked cells to further take unspecific binding into consideration.

For the determination of the CD34+CD45dim cells, the gated MNCs were further analysed in a side scatter (SSC)/CD34 PE plot. The CD34+ cells were gated and analysed in a CD34 PE/CD45 PECy7 plot in which the CD45dim cells were gated and counted. The control tube with IsoClonic-Control PE instead of anti-CD34 PE was analysed in the same way to define the gates and correct for unspecific binding. The lymphocytes were gated in the SSC/forward scatter (FSC) plot and the number of lymphocytes were used as the denominator in the calculation of the relative amount of CD34+CD45dim cells.

The flow cytometry of whole blood samples was performed on a Coulter Navios flow cytometer (Beckman Coulter Inc., Fullerton CA, USA). Leucocytes were gated in an FSC/SSC plot, and the gated cells were analyzed in a CD34/SSC plot. The gated CD34+ cells were analyzed in a CD34/CD45 plot, and the CD34+CD45dim cells were gated and counted. The control sample with IsoClonic-Control PE was analysed in the same way to define the gates and correct for unspecific binding. The CD34+CD45dim counts were converted to absolute concentrations based on the equivalent counts of flourosphere beads according to the manufacturer's instructions.

PLATELET FUNCTION

Platelet activation

Platelet activation was investigated by measuring the surface marker CD62P (from α granules) and binding of PAC1 (antibody that binds specifically to the activation induced conformational epitope on GPIIb-IIIa). EDTA stabilized whole blood samples were incubated with the following conjugated antibodies purchased from BD Biosciences (San Jose, CA): PAC1 FITCH, anti-CD62P PE, anti-CD41 PE-Texas red (ECD) and anti-CD45 PE-Cyanin 5.1 (PC5). Relevant isotype control antibodies were used as controls. The samples were analysed by flow cytometry (Coulter Navios, Beckman Coulter Inc.). Platelets were identified in logarithmic/SS plots with 10000 CD41+ counts in the platelet gate. The results are presented as proportion of stained cells as defined by the appropriate isotype control.

Thromboelastography (TEG)

Clot formation was assessed in citrated whole blood using a TEG 5000 Haemostasis Analyser System (Haemonetics Corp, Braintree MA, USA) according to the manufacturer's recommendations. The variables reported were reaction time (R – reflecting rate of initial fibrin formation), alpha angle (α – reflecting clot formation kinetics) and maximum amplitude (MA – reflecting maximum clot strength).[21]

Multiplate assay

Whole blood platelet aggregometry was assessed using the Multiplate® (Dynabyte Medical, Munich, Germany) device measuring increased impedance (expressed as the area under the curve (AUC) of increasing impedance over time) in whole blood as a consequence of aggregation of stimulated platelets on the electrodes.[22] Platelets were stimulated according to the manufacturer's instructions with adenosine-diphosphate (ADP, final concentration 6.5 $\mu mol \cdot L^{-1}$), arachidonic acid (ASPI, final concentration 0.5 $mmol \cdot L^{-1}$) and thrombin receptor-activating peptide 6 (TRAP, final concentration 32 $\mu mol \cdot L^{-1}$).

STATISTICAL ANALYSIS

The difference between pre- and post-HBO treatment values of CD34+CD45 dim cells, of Aldefluor® positive cells, and of the platelet activation and function tests were tested for significance by the Wilcoxon matched-pairs signed-ranks test. $P > 0.05$ was considered not significant (n.s.). The putative cumulative effect of the first 15 HBO exposures on the CD34+CD45dim counts was analysed with a linear mixed effects model using Statistical Analysis System (SAS/STAT 9.2) software.

Results

Six of 10 enrolled patients (1, 2, 4, 6, 7 and 10) completed the full treatment course (29–30) within a period of 42–49 days. For patients 1, 2 and 10, the duration beyond six weeks (42 days) was due to illness or cancellation of treatments due to acute situations. Four patients (3, 5, 8 and 9) dropped out at some point after the fifteenth exposure or did not comply with the study treatment period (a duration of more than 50 days in total was considered as non-compliance, which was the case for patients 5 and 9). The whole blood counting of CD34+CD45dim cells around the first HBO exposure of patient 9 failed, and thus patient 9 is excluded from Figure 2. Reasons for non-compliance were lack of physical and mental energy.

MEASUREMENT OF CD34+CD45dim CELLS

The results given are the mean of duplicate measurements. Results from the single platform whole blood analyses of absolute numbers of CD34+CD45dim cells are shown in Figure 2. We found a tendency for a rise in CD34+CD45dim

Figure 2

CD34+CD45dim cells per mL blood. Results from absolute counting in whole blood samples. Significance tests are the results from Wilcoxon matched-pairs signed-ranks tests for difference between results on adjoining vertical lines (n.s. = not significant)

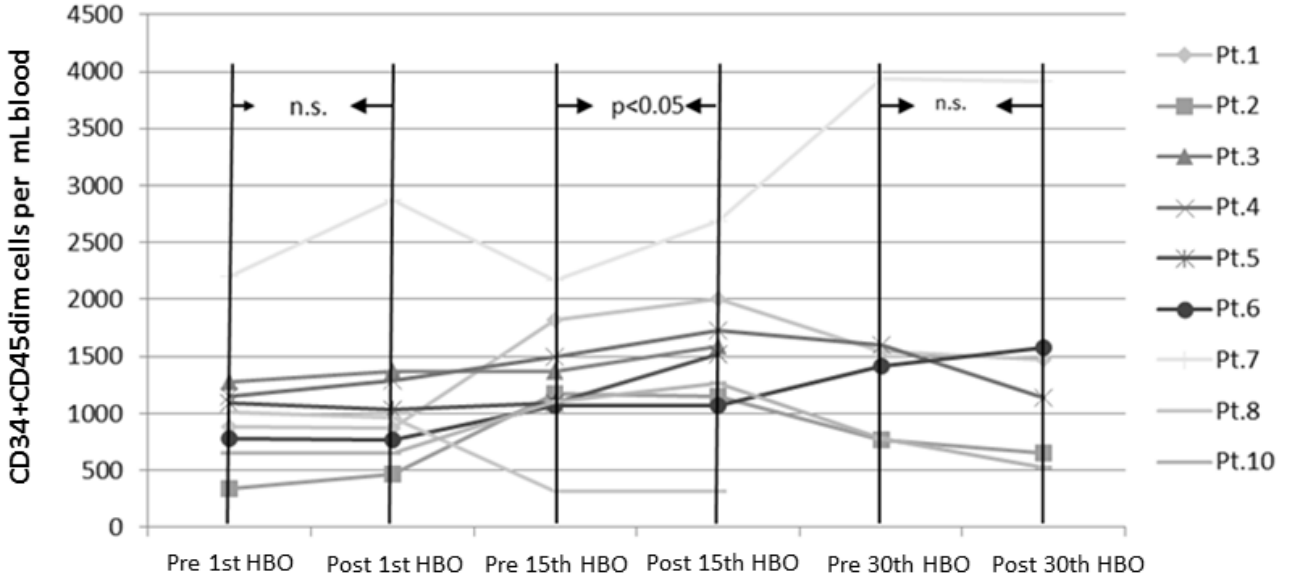
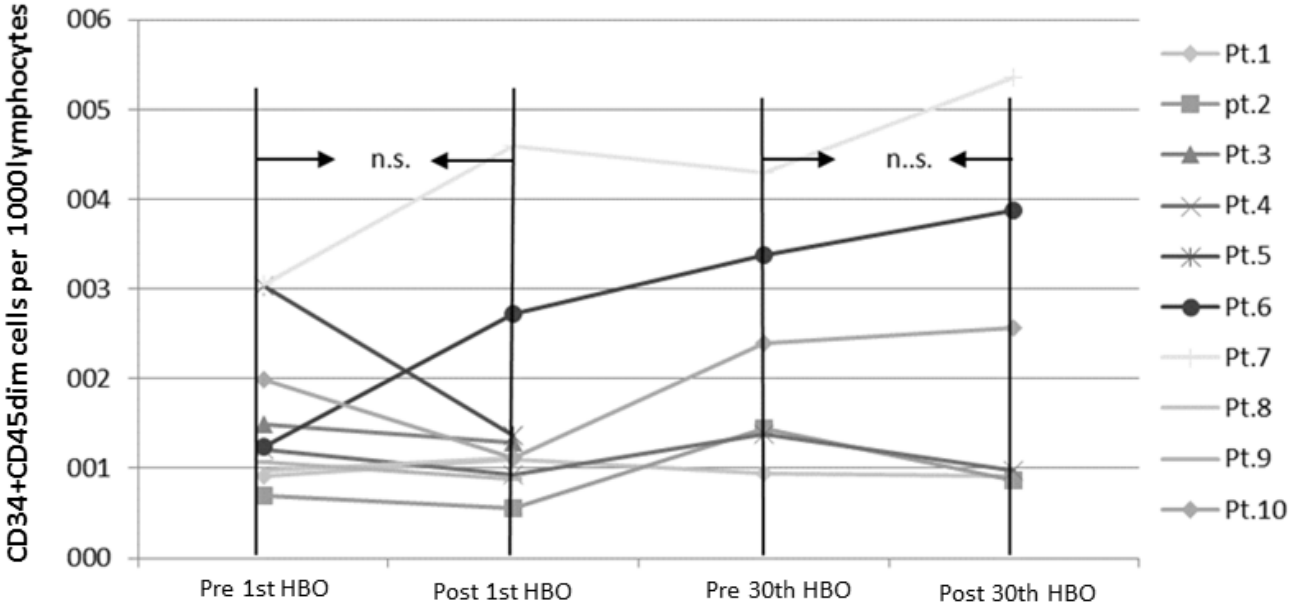


Figure 3

CD34+CD45dim cell fraction of lymphocytes. Results from analysis of the mononuclear cell suspensions. Significance tests are the results from Wilcoxon matched-pairs signed-ranks tests for difference between results on adjoining vertical lines (n.s. = not significant)



counts from before to immediately after a given HBO exposure. However, except for around the fifteenth exposure, the changes did not reach statistical significance, and after the thirtieth exposure there was a small reduction in CD34+CD45dim counts. In the six patients who completed the full treatment course, there was a rise in CD34+CD45dim counts from before the first to after the thirtieth exposure but it was weak and did not reach statistical significance. The dropping-out of four of 10 patients precluded a valid statistical analysis of the results after the thirtieth HBO exposure since a drop-out bias cannot be excluded. However, all patients completed 15 HBO exposures, and we found a significant rise in CD34+CD45dim counts after the fifteenth versus before the first exposure using a linear mixed effect model (Table 3). The upper 97.5% limit of the rise in CD34+CD45dim counts was 931 cells·ml^{-1}, i.e., below a doubling of the counts recorded before the first HBO exposure, the mean of which was 1101 CD34+CD45dim

Table 3

Analysis of the CD34+CD45dim number of cells per mL blood around the first and the fifteenth HBO treatment with a linear mixed effects model with fixed effects for run (1 or 15) and treatment (pre or post) and their interaction. The random effects follow a variance component structure with random effects for patients and patient and run combinations. Missing data are assumed to be missing at random. The mean number of CD34+CD45dim cells per mL blood before the first HBO treatment was 1101. Comparisons, single-step adjusted for multiple comparisons. 2.5% and 97.5%, lower and upper confidence interval limits

Comparison	Estimate	2.5%	97.5%	*P*-value
Post 15 – pre 1	498.39	65.08	931.71	0.018
Post 1 – pre 1	117.27	-22.43	256.96	0.128
Post 15 – pre 15	201.11	47.42	354.80	0.005

Table 4

Platelet function by multiplate analyzer and thromboelastograph. ADP = adenosine triphosphate; ASPI = arachidonic acid; AUC = area under curve; MA = maximal amplitude; R = reaction time(s); TRAP = thrombin receptor activating peptide 6

Analysis	% change after versus before 1st HBO treatment	
	Mean (SD)	Wilcoxon
Multiplate Analyzer		
ASPI (AUC)	20 (45)	n.s.
ADP (AUC)	-4.4 (23)	n.s.
TRAP (AUC)	6.5 (24)	n.s.
Thromboelastograph		
R (s)	0.7 (21)	n.s.
Alpha angle (degree)	0.05 (5.8)	n.s.
MA (mm)	2.2 (5.7)	n.s.

cells·mL^{-1}. However, the lower 2.5% limit of the rise in CD34+CD45dim counts was 65, which is compatible with the notion that repeated HBO exposures might induce a modest rise in the CD34+CD45dim counts.

The changes in the CD34+CD45dim fraction of lymphocytes from before a given HBO exposure to immediately after varies between a modest rise in some patients and a modest fall in others (Figure 3). However, neither the changes around the first HBO exposure nor the changes around the thirtieth exposure reach statistical significance, thus confirming the results from the analysis of whole blood.

The mean (SD) change in CD34+CD45dim cells measured immediately after versus before a given HBO exposure was 4.2% (17%) (n = 23) in the absolute CD34+CD45dim measurements and 0.2% (42%) (n = 16) in the relative CD34+CD45dim measurements. Neither of these changes were significantly different from 0%.

MEASUREMENT OF ALDEFLUOR POSITIVE CELLS

The changes in Aldefluor® positive cells expressed as fraction of lymphocytes are shown in Figure 4. We found that the second of the duplicate measurements of Aldefluor® positive cells was significantly lower, 51% (21%), than the first measurement, presumably due to leakage from the cells of some of the ALDH converted intracellular Aldefluor® during the time lapse of 30–45 minutes between sample analysis. Thus, the results given are from only the first of the duplicate measurements. Only insignificant changes are imposed by the first HBO exposure (10 patients) and the thirtieth HBO exposure (six patients). The CD34-negative subpopulations of Aldefluor® positive cells, including possible MSCs, are given as white columns in Figure 4. Only a minute fraction of Aldefluor® positive cells was CD34 negative, and it was not significantly influenced by the HBO treatment.

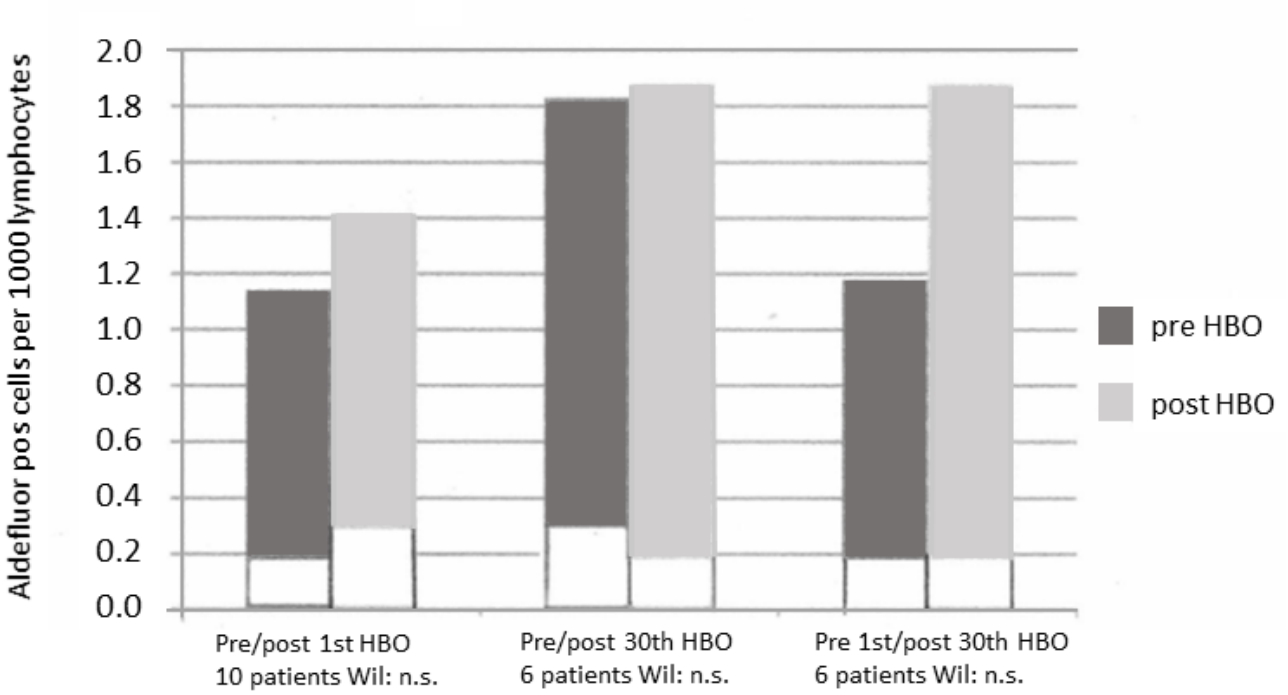
Platelet measurements

Results from measurements of platelet function before and after the first HBO exposure are shown in Table 4. The multiplate analyzer results indicate that no statistically significant changes were seen in aggregation efficiency after various activators as measured by the AUC. Additionally, no statistically significant changes were seen after versus before the first HBO exposure in the clot formation as measured by the thromboelastograph.

In the flow cytometric measurement of activation markers shown in Figure 5, we could not detect a statistically significant change in the fraction of platelets expressing the activation markers post-HBO versus pre-HBO taking all ten patients into consideration. However, excluding patients 4, 5, and 9 who all had pretreatment values below 2% CD62 positive platelets and below 5% PAC positive platelets, the remaining seven patients had a statistically significant fall in the fraction of activated platelets ($P < 0.02$ for both activation markers).

Figure 4

Aldefluor® positive cell fraction of lymphocytes. Results from analysis of the mononuclear cell suspensions. Wil: n.s. stands for: Wilcoxon matched-pairs signed-ranks tests for difference between results in adjoining columns (n.s. = not significant). The white areas at the bottom of each column indicates the amounts of the Aldefluor® positive cells which were CD34 negative



Discussion

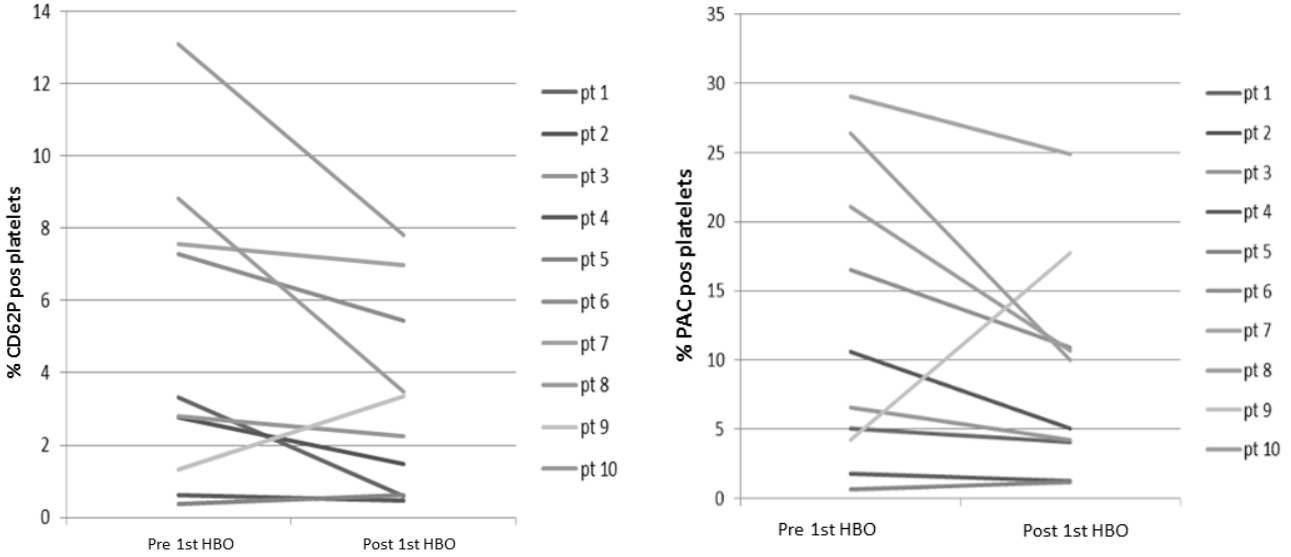
The present study demonstrated a weak and insignificant tendency toward mobilization of CD34+CD45dim cells after a single exposure to 2.4 ATA HBO in both absolute and relative values. Because four patients did not complete the scheduled 30 HBO exposures, a putative additive effect of the preceding HBO exposures could only be analyzed in a statistically valid way by comparing the absolute CD34+ counts before the first HBO exposure to the CD34+ counts after the fifteenth HBO exposure. In this case, it was less than a doubling but still more than zero.

The drop-out of four patients in the present study may well have impacted the results due to decreased statistical power, which may have contributed to the contrast between our findings and two of the studies by Thom's research group.[4,10] In 2006 and 2014, they reported, in larger patient populations qualitatively similar to the present one, a more than doubling of the CD34+CD45dim population after only one HBO exposure.[4,10] Also, they found increases of approximately 8- and 20- fold after 20 HBO exposures at 2.0 and 2.5 ATA, respectively. In 2011, Thom et al.[11] reported a more than doubling after one HBO exposure in patients with diabetic ulcers, but, in accordance with the present study, they did not find a cumulative effect of repeated exposures (up to 20 exposures) as in the other two studies. This difference from the two previous studies was interpreted by the authors as caused by different diagnoses. For completeness, another study investigated HBO treatment in chronic wound patients and reported increases in values of circulating CD34 cells relative to blood cells of the same order of magnitude as the findings by Thom et al. No absolute values were given.[23]

In contrast, Shandley et al., reported only a non-significant trend towards increasing stem cell percentage with increasing number of HBO treatments after traumatic brain injury and correlated CD34+CD133+nestin+cells with different outcome measures of cognitive performance.[24] The authors found that improvement in clinical results correlated with stem cell mobilization in the HBO treated group, but not in the sham treated group. However, although, the values of circulating SPCs are difficult to interpret and no definite values are given, overall, they only found minor and non-significant trends towards increasing stem cell percentage with increasing number of treatments. Also, it appears that for both HBO and sham treated patients, there was an approximately equal distribution between increase/no change/decrease in stem cell mobilization. Thus, their conclusions regarding circulating SPCs are in line with our findings.

The contradictory findings between the studies are hard to explain. It could be argued that different diseases could possibly affect the results, an assumption supported by the studies by Thom et al. Nevertheless, even in similar patient populations, the reported data are very different. Although undocumented, there are several unknown factors that could possibly affect the results, e.g., the kinetic and circulation time of cells potentially recruited into the development of

Figure 5
Fraction of activated platelets. Flow cytometric analysis of the fraction of platelets expressing the activation markers: CD62P and PAC-1 positivity, pre and post first HBO treatment



new tissue and the possible influence of the frequency of change in oxygen as well as the overall dose and delivery regimen. Also, one could speculate that the use of air breaks during HBO treatment sessions, creating an oscillation in tissue oxygen partial pressure, could have an impact on stem cell responses as normobaric oxygen oscillation has been shown to affect hypoxia-inducible factor 1a (HIF-1a) and erythropoietin (EPO) expression levels.[25] We did not use frequent air breaks in our setting. In the related studies, use of air breaks is not mentioned.[4,10,11]

In addition, differences/inconsistencies in the reporting make the results difficult to interpret and compare, e.g., the lack of absolute values,[23,24] a factor 8 to 10 difference in CD34+ counts at baseline ranging from 0.2% of lymphocytes to 0.2% of whole blood cells (WBC)[4,10,11] and statements regarding surface marker expression on EPCs versus HSCs that contradicts the guidelines from ISHAGE.[4,20]

In the present study, we used two different methods – a MNC separation technique and a whole blood method – to determine the CD34+CD45dim population and found results that were consistent between the methods. In addition, we detected cells with high ALDH activity as a marker for stem cells of any kind. We demonstrated a trend towards an approximately 50% increase in ALDH positive cells from before the first to after the thirtieth HBO exposure, although the increase was not statistically significant. Again, the drop-outs reduced the statistical power, but still our observations are very far from the 8- or 20-fold increase in circulating SPCs described in some previous studies.[4,10] Four of the ten patients in our study were smokers, which may possibly have contributed to the overall results. Cigarette smoke extract has been demonstrated to inhibit MSC migration and differentiation in vitro,[26] and cigarette smokers have lower EPC numbers in circulating blood and bone marrow post-acute myocardial infarction.[27]

With respect to the putative EPCs, it should be noted that the biological significance of circulating bone marrow derived EPCs recently has been questioned. Thus, genetic fate mapping has shown that the endothelial stem/progenitor cells involved in adult angiogenesis are not bone marrow derived but derive from local tissue resident cells.[28] Furthermore, Fang et al.[29] have provided evidence for adult vascular endothelial stem cells that reside locally in the blood vessel wall endothelium.

There have been diverging results regarding whether HBO may induce a hypercoagulation state and/or platelet activation.[15–18] In the present study, we used a whole blood viscoelastic hemostatic test, the TEG, a whole blood WB aggregometry analyzer, the Multiplate, and flow cytometric detection of platelet activation markers. In general, we found no alterations in any of these tests comparing post-HBO values to pre-HBO values. Interestingly, seven of the ten patients had at baseline more than 2% CD62P positive platelets and more than 5% PAC-1 positive platelets, reflecting increased platelet activation before the first HBO exposure. In these patients, we found a significant decrease in activated platelets after the first HBO exposure. The result is only indicative of a possible action of HBO and should be confirmed in a larger study. However, if HBO treatment indeed decreases a heightened platelet activation state, the treatment would hamper the migration of activated platelets to areas of inflammation. No concomitant alterations were detected in the functional tests, possibly because of lack of sensitivity at this level.

Conclusions

We found a minor statistically significant mobilizing effect on the bone marrow derived stem/progenitor cell content in peripheral blood after 15 HBO treatments (n = 10 patients), but no effect after 30 treatments (n = 6 patients). However, because of the low number of patients we cannot confidentially prove or disprove the null hypothesis. The possibility that HBO treatment reduces the number of activated platelets could not be demonstrated nor excluded.

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Assessment of sensory sensitivity through critical flicker fusion frequency thresholds after a maximum voluntary apnoea

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Key words
Brain; Breath-hold diving; Exercise; Fatigue; Hypoxia

Abstract
(de Asís Fernandez F, González-Mohino F, González-Ravé J. Assessment of sensory sensitivity through critical flicker fusion frequency thresholds after a maximum voluntary apnoea. Diving and Hyperbaric Medicine. 2019 September 30;49(3):186–191. doi: 10.28920/dhm49.3.186-191. PMID: 31523793.)
Introduction: The influence of acute exercise on sensory sensitivity (SS) differs according to the type and duration of exercise performed. In the present study, we assessed changes on SS soon after a maximal dynamic apnoea.
Methods: Thirty-nine experienced male breath-hold divers were recruited. Critical flicker fusion frequency (CFFF) thresholds were used to measure SS. Thresholds were determined before and after a maximal dynamic apnoea. Immediately after surfacing, heart rate and oxygen saturation (SpO_2) were recorded for two minutes.
Results: After maximal dynamic apnoea, SpO_2 was significantly decreased (from mean 97.3% pre-dive to mean 63.1% post-dive; $P < 0.0001$; $\eta 2$ $P = 0.86$), but this acute hypoxaemia did not trigger changes in SS (post-dive value 102% of baseline; $P = 0.22$; $\eta 2$ $P = 0.03$). Pearson correlation analysis revealed a moderate association between SS with swimming speed ($r = 0.423$) and apnoea time ($r = -0.404$).
Conclusions: A maximal dynamic apnoea did not produce changes in central nervous system fatigue or cortical arousal. We found no relationship between the hypoxaemia level reached after a maximal apnoea and changes in the CFFF thresholds. This study suggests that the time of exposure to hypoxia during a maximal voluntary apnoea is not enough to produce changes in SS.

Introduction

Critical flicker fusion frequency (CFFF) is considered a quantitative and validated measure of sensory sensitivity (SS), and the CFFF threshold is of interest in sport, as it can be used to determine the degree of CNS fatigue and cortical arousal.[1–4] Tomporowski et al. noted that aerobic and anaerobic exercise at moderate intensities seemed to produce improvements in cognitive performance, while an intense, brief and exhaustive bout of anaerobic exercise did not affect cognitive function.[5] However, sub-maximal exercise taken over a long period, leading to dehydration or/and depletion of energy substrates, seems to decrease both information processing and memory functions.[5] Thus, if we consider breath-hold diving as an intense, brief and exhaustive anaerobic form of exercise, we could hypothesize that apnoea training would not produce changes in the SS, although it must be considered that this type of exercise is considerably different from those examined in the studies above.

Decreased muscular strength, coordination impairment, physical and mental fatigue and somnolence are several functional disorders that can occur due to hypoxia; they develop in proportion to the demand for oxygen and intensify with the duration of hypoxia.[6] Previous studies have analyzed the influence of a stay at altitude ranging from 4000 m to 5500 m, suggesting SS changes that may be attributed to repeated forays to high altitudes.[7–9] CFFF measurements have been made during routine testing of hypoxia tolerance in pilots and skydivers, and these findings suggest that the intermittent hypoxia experienced does not cause changes in SS.[10,11] CFFF has also been used in diving studies. It is thought that post-dive fatigue and an associated reduction in alertness could be caused by one or all of three factors: the effects of nitrogen, oxygen or circulating bubbles on the body after a dive.[12–14]

The exposure to short-term intermittent hypoxia, frequently experienced by trained breath-hold divers, leads to sustained sympathetic activation. However, it is not known if apnoea training can produce changes in SS, either via central nervous system (CNS) fatigue or by increased cortical arousal.[15] The present study aimed to assess changes in SS (mainly cortical arousal or CNS fatigue) after a maximal dynamic apnoea, made by swimming as far underwater as

Figure 1
Breath-hold diver performing CFFF test: undertaken before and after maximal dynamic apnoea

possible during a breath-hold in a swimming pool with fins. The null hypothesis was that soon after a maximal dynamic apnoea there would be no changes in SS.

Methods

The protocol was conducted in accordance with the Declaration of Helsinki and was approved by the institutional Human Research Ethics Committee (UAM-CEI-70-1257).[16]

PARTICIPANTS

Thirty-nine male breath-hold divers were recruited in this multicenter study from different Spanish locations. Their mean (SD) age was 38 (7) years, experience in competitive apnoea was 5 (3) years and their personal best in dynamic apnoea with bi-fins was 102 (19) horizontal metres. Divers were informed of the procedures involved in the trial, including the benefits and risks, prior to signing the informed consent document. Participants with a history of epilepsy were excluded from the study.

CRITICAL FLICKER FUSION FREQUENCY THRESHOLDS

We assessed CFFF thresholds using a Lafayette Instrument Flicker Fusion Control Unit (Lafayette Instrument, Lafayette IN, USA). This device consists of two white light emitting diodes (58 $cd \cdot m^2$) that are simultaneously displayed in the system, one for the left eye and one for the right. The diodes are separated by 2.75 cm, with a diode-to-eye distance of 15 cm and a viewing angle of 1.9 degrees. The interior of the equipment is painted matte black to minimize interference. The flicker frequency increment (1 $Hz \cdot sec^{-1}$) changed in two ways: either it increased (from 0 to 100 Hz) until the subject perceived fusion or decreased (from 100 to 0 Hz) until flicker was detected. After a fovea binocular fixation, participants were required to respond by pressing a button upon identification of the visual flicker (descending frequency) and the fusion (ascending frequency) thresholds.

Before the experiment, subjects performed as many practice trials as necessary to familiarize themselves with the CFFF test. During the test, three ascending and three descending trials were performed alternately. The mean of the six values, representing the classical CFFF thresholds, was calculated for each subject.

OXYGEN SATURATION, SWIMMING SPEED AND APNOEA TIME

We used a finger probe pulse-oximeter (NoninPalmSAT® 2500, Nonin Medical, Plymouth MN, USA) to detect changes in oxygen saturation (SpO_2) and heart rate (HR). During the measurement, a green signal indicated good perfusion, while a red light denoted bad perfusion. Only data collected during good perfusion readings were analyzed. Lost motor control in the diver was recorded as a manifestation of symptomatic hypoxia.[17] To assess average swimming speed, we recorded the time and distance reached during dynamic apnoea.

PROCEDURES

The examinations were conducted in a quiet, temperature-regulated and humidity-controlled room, close to the swimming pool (24 ± 1ºC, relative humidity 80–90%). The tests were conducted by a single evaluator who had not participated in the selection process.

Baseline characteristics, SpO_2 and CFFF, were obtained and participants were seated in front of the CFFF viewing chamber to determine CFFF thresholds, using the protocol described previously (Figure 1). The divers were then asked to perform a maximal dynamic apnoea with bi-fins in a 25 m pool. A safety diver accompanied the divers during the attempt, as during competitions. HR and SpO_2 were recorded immediately on surfacing at five second intervals for two minutes. Average swimming speed was calculated as described. Finally, three minutes after the maximal dynamic apnoea, the CFFF thresholds were measured as per the pre-dive protocol (Figure 1).

STATISTICS

G*Power 3.1.7[18] statistical software (Heinrich-Heine-Universität, Düsseldorf, Germany) was used to calculate the sample size needed to complete this study. Based on alpha = 0.05 and an assumed effect size of 0.42 (based on pilot study data; $n = 12$), for 80% power we calculated that a total sample size of 37 participants would be necessary.

All experimental data analysis was performed using IBM SPSS Statistics for Windows, Version 21.0 (IBM Corp., Armonk, NY, USA). The statistical analyses were conducted at a 95% confidence level; a *P*-value of less than 0.05 was

Figure 2
Correlation plot demonstrating the relationship between CFFF (Hz), pre- and post-apnoea measurements and the average swimming speed reached (r = 0.423, $P < 0.05$)

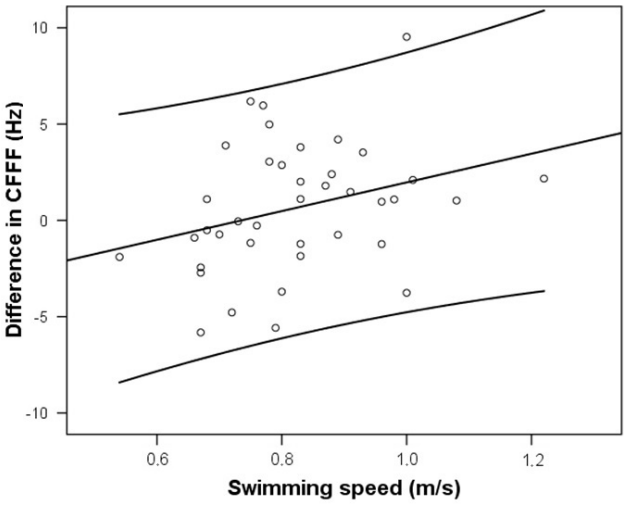
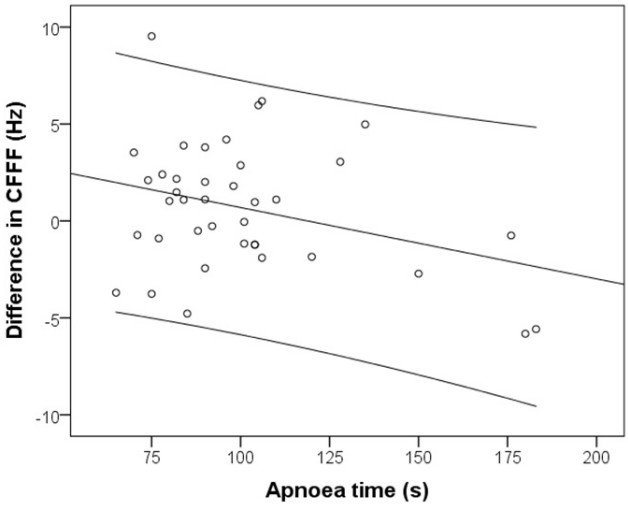


Figure 3
Correlation plot demonstrating the relationship between CFFF (Hz), pre- and post-apnoea measurements and total apnea time (r = -0.404, $P < 0.05$)



considered statistically significant. We expressed our results as means and standard deviations (SD) with 95% confidence intervals. We confirmed the normality of the data using the Shapiro-Wilk test.

Student's *t*-test (one sample, two-tailed) was used to analyze changes in CFFF thresholds and SpO_2 between baseline and post-apnoea; we also assumed partial η^2 as a measure of the effect sizes of exercise on the CFFF. Effect sizes (Cohen's d) were calculated for the outcome variables. According to Cohen's method, the magnitude of the effect is classified as small (0.20–0.49), medium (0.50–0.79), or large (≥ 0.8).[19] Taking the baseline value as 100%, percentage changes were calculated, allowing an appreciation of the magnitude of CFFF change between each measurement rather than the absolute values.

The relationships between sensory sensitivity, swimming speed and apnoea time were examined using Pearson correlation coefficients. A Pearson correlation coefficient > 0.60, between 0.30 and 0.60, and < 0.30 indicated high, medium, and low correlations, respectively.[20]

Results

SENSORY SENSITIVITY AND OXYGEN SATURATION

CFFF and SpO_2 reached after the maximal dynamic apnoea are illustrated in Table 1a. Compared to the baseline, there was a significant decrease of SpO_2 during apnoea, from 97.1 (0.7) to 63.1% (13.7) ($P < 0.0001$; η^2 $P = 0.86$). However, CFFF measurements made three minutes after the maximal dynamic apnoea were not statistically different from the baseline values (102.0%; $P = 0.22$; η^2 $P = 0.03$).

Upon subgrouping subjects (Table 1b), adoption of the lost motor control criteria used to determine hypoxia effects revealed that SaO_2 decreased from 97.3 (0.7) to 66.1% (13.1) in divers with no hypoxic effect ($n = 31$) and from 96.8 (0.9) to 49.2% (7.5) in divers with lost motor control ($n = 7$). In both groups, CFFF results were not statistically different from the baseline value: 35.3 (4.4) to 35.9 Hz (4.4) in divers with no hypoxic effect (101.7%; $P = 0.22$; η^2 $P = 0.04$) and 30.5 (7.7) to 30.9 Hz (4.3) in divers with lost motor control (101.3%, $P = 0.77$; η^2 $P = 0.01$).

CORRELATION ANALYSES

Pearson correlation showed only a small relationship between the SpO_2 values reached during the maximal dynamic apnoea and changes in SS (r = 0.268, $P < 0.05$). There was a moderate association between SS with swimming speed (r = 0.423, $P < 0.05$; Figure 2) and apnoea time (r = -0.404, $P < 0.05$; Figure 3).

Discussion

This study analyzed the effect of maximal dynamic apnoea on SS using CFFF. If maximal apnoea leading to exhaustion does induce a transitory CNS fatigue, a decrease in SS should be observed.[21] Alternatively, if apnoea induces an increase in cortical arousal, an increase in SS should be observed. Our findings showed that no changes were observed in CNS fatigue or cortical arousal after a maximal dynamic apnoea. Thus, the induced fatigue during a maximal apnoea, if any, is most likely to be linked to peripheral fatigue (in the muscle) or perceived fatigue (exertion tolerance) and not due to CNS fatigue. In addition, there is no evidence that repeated hypoxic syncope, caused by apnoea training, has long-term effects on cognitive functions or neurological effects.[22]

Table 1

(a) Percentage variation of CFFF and oxygen saturation (SpO_2) between pre- and post-apnoea measurements. (b) Participants are subgrouped into no hypoxic effects (n = 32) and with loss motor control (LMC) (n = 7). *** indicates $P < 0.0001$

Table 1 (a)		Pre-apnoea	Post-apnoea		Sig	η^2P
		Mean (SD)	Mean (SD)	% from baseline		
Participants (n = 39)	CFFF threshold (Hz)	34.4 (5.3)	35.1 (5.2)	102.0	0.221	0.039
	Oxygen saturation (%)	97.1 (0.7)	63.1 (13.7)		***	0.862
Table 1 (b)		**Pre-apnoea**	**Post-apnoea**		**Sig**	**η^2P**
		Mean (SD)	**Mean (SD)**	**% from baseline**		
No hypoxic effects (n = 32)	CFFF threshold (Hz)	35.3 (4.4)	35.9 (4.4)	101.7	0.223	0.048
	Oxygen saturation (%)	97.3 (0.7)	66.1 (13.1)		***	0.994
Loss motor control (n = 7)	CFFF threshold (Hz)	30.5 (7.7)	30.9 (4.3)	101.3	0.770	0.015
	Oxygen saturation (%)	96.8 (0.9)	49.2 (7.5)		***	0.998

During breath-hold diving, progressive hypoxaemia stimulates the respiratory centers in the brain and in our study, severe hypoxaemia was noted in all divers after the maximal apnoea swim.[23] One of our main findings is that there was no relationship between the levels of hypoxaemia reached after a maximal apnoea (even in divers who lost motor control) with changes in the CFFF thresholds measured three minutes later. However, it should be noted that although severe, the hypoxaemia experienced during an apnoea swim is of very short duration in comparison to the exposure that mountaineers or pilots undergo.[9,10] If we consider apnoea as an intense, brief and exhaustive anaerobic exercise, the findings of the current study support the hypothesis that the influence of acute exercise on cognitive function differs according to the type and duration of exercise performed.[5]

We also noted a moderate, inverse relationship between apnoea time and SS. This finding could support the hypothesis that it is the time and not the intensity of exposure to hypoxia that is the factor crucial to the production of SS changes. A similar conclusion was reached by Cavalade, who used CFFF to measure the effects of hypoxia on skydivers, and suggested that repeated jumps above 4,000 m were not long enough and therefore of great enough hypoxic stimulus to alter SS.[11] It is possible that the time of exposure to hypoxia is critical to produce CNS changes, but neither our data nor that in the literature have definitively established this.

CFFF thresholds are affected by both non-sensory and sensory factors.[1] During maximal apnoea, divers can be exposed to factors other than hypoxia, including hypercapnia, muscular acidosis, mental effort, stress or fear. Due to the correlations determined in our study, we could suggest that the divers who reached a higher underwater swimming speed also produced a higher increase in SS. As such, it could be speculated that faster divers had a greater stimulation of the sympathetic nervous system due to a requested higher inter- and intramuscular coordination and processing speed. This would be in accordance with a previous study, which found that short submaximal and repeated apnoeas in trained divers are powerful enough to intensify sympathetic nervous system activity.[24]

CFFF could be a practical substitute for various psychological measures in assessing SS in a diving/hyperbaric environment.[25] As mentioned previously, changes in nitrogen or oxygen concentration could be considered to explain the variations in post-dive SS. Lafère stated that the changes in perceived fatigue level after a single dive were significantly lower when divers breathed enriched air nitrox compared to air dives.[14] Balestra found that inert gas narcosis produced a cerebral impairment that then persisted for at least 30 minutes after surfacing from a 20 min dive to 33 m.[12] However, increasing the oxygen fraction improved cognitive competence during a dive to 24 m due to the reduced narcotic effects of the nitrogen fraction.[13]

Scuba diving involves complex phenomena in the functional modifications of the nervous system according to the type of gas used for the dive; although freedivers who perform deep apnoeas may be affected by episodes of narcosis, the participants involved in our study (in a swimming pool) were not.[14,26] On this basis, we must suggest that the results from

the present study should not be applied to breath hold divers who perform deep dives.

Changes in blood pressure or blood flow in the freedivers during the maximum dynamic apnoea were not evaluated. An increase in blood pressure is associated with disruptions in neurovascular coupling, which leads to a decrease in vascular reserve capacity and can cause cognitive changes.[27] Factors other than perfusion or autonomic failure have also been proposed to contribute to cognitive decline.[28] In view of the above, in future studies, analysis of blood pressure and brain blood flow should be included in order to clarify the changes produced in the SS after a maximal apnea.

Clearly there are limitations in the techniques we used when trying to measure hypoxaemia. It has been suggested that a finger probe is inferior to an ear probe for measuring SpO_2 during apnoea, but the use of the former is recommended in the patient with poor peripheral perfusion, as, for example, in a diver affected by limited peripheral blood flow triggered by the diving response.[29,30] Another methodological limitation was that the average speed was calculated by total distance and apnoea time during the maximal dynamic apnoea. No consideration could made for a change in speed, for example during a brief sprint.

In conclusion, maximal dynamic apnoea did not produce changes in CNS fatigue or cortical arousal. In addition, no relationship between hypoxaemia levels reached after maximal apnoea and changes in the CFFF thresholds was found. This study suggests that the time of exposure to hypoxia, during a maximal voluntary apnoea, is not enough to produce sensory sensitivity changes.

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Snorkelling and breath-hold diving fatalities in Australia, 2001 to 2013. Demographics, characteristics and chain of events

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Breath-hold diving; DAN – Divers Alert Network; Diving deaths; Fatalities; Immersion; Snorkelling

Abstract
(Lippmann J. Snorkelling and breath-hold diving fatalities in Australia, 2001 to 2013. Demographics, characteristics and chain of events. Diving and Hyperbaric Medicine. 2019 September 30;49(3):192–203. doi: 10.28920/dhm49.3.192-203. PMID: 31523794.)
Introduction: The aim of this study was to identify characteristics of victims of fatal snorkelling and breath-hold diving accidents in Australia from 2001–2013, inclusive, to determine underlying factors and risks associated with such activities and inform appropriate countermeasures.
Methods: The National Coronial Information System (NCIS) was searched to identify snorkelling and breath-hold diving-related cases reported to Australian coroners for the years 2001–2013, inclusive. Coronial data in the form of findings, witness and police reports, medical histories and autopsies were collected and collated, and descriptive statistics were used to analyse these data. A chain of events analysis was used to determine the likely sequence of events.
Results: There were 175 identified snorkelling-related fatalities during the study period. Most victims were middle-aged males (mean age 49 years). Pre-existing health conditions were possible contributors to 41% of the deaths, the main being ischaemic heart disease. The majority of deaths occurred in Queensland in inexperienced snorkellers, often in commercial settings. The victim's plight often went unnoticed as they were alone, or poorly supervised, when the incident occurred. Apnoeic hypoxia appeared to have been associated with at least 12.5% of the deaths. The main disabling injuries were asphyxia (40%) and cardiac incidents (35%).
Conclusion: Human factors, such as chronic health conditions, poor skills and inexperience and poor planning can play a substantial role throughout the chain of events leading to a snorkelling fatality. It is important to educate the community, doctors and dive industry professionals about potential problems associated with the interaction between certain health-related conditions, especially cardiovascular conditions, and snorkelling. Close supervision is strongly recommended for inexperienced snorkellers due to their likely poor skills, as well as for experienced breath-hold divers due to the potential for apnoeic hypoxia.

Introduction

Snorkelling involves a person breathing through a shaped breathing tube (snorkel) while swimming. A mask for underwater vision, and, often, fins for propulsion are also worn. In addition to swimming on the surface (surface snorkelling), snorkelling may also involve breath-hold diving underwater.

Although the origins of snorkelling are unclear, archaeological evidence suggests that humans were breath-hold diving for shells, and probably food, as early as 4500 BC.[1] Snorkelling has become a popular recreational activity in parts of Australia, especially on the tropical reefs of northern Queensland and Western Australia. There is a dearth of reliable data on the level of snorkelling activity nationwide. A recent report estimated that there were 0.4 million 'frequent snorkellers' (at least once a month) nationally.[2] However, this was based on a very small sample size and is likely to be unreliable; in the author's view, an overestimate of the activity of Australian residents. There is little doubt that the bulk of the snorkelling activity in Australia occurs in Queensland. A survey of domestic and international visitors to Queensland estimated that approximately 1.2 million tourists (half of them from overseas) performed an estimated total of 2.3 million individual snorkel dives (both surface and breath-hold) in Queensland over the 12-month period from April 2006.[3]

Snorkelling can involve a variety of environmental, skills-related, physical, psychological and medical challenges and inevitably results in some associated morbidity and mortality.[4] The Australasian Diving Safety Foundation (ADSF), and before it, the Divers Alert Network Asia-Pacific (DAN AP) and Project Stickybeak,[5] have compiled and maintained a database of identified diving-related fatalities

Table 1
Age measures (in years) of snorkelling victims, 1965–2013

Measure	All (*n* = 337)	Male (*n* = 289)	Female (*n* = 48)
Mean (SD)	43.4 (19.6)	42.3 (19.6)	50 (18.5)
Median (IQR)	40 (26, 61)	39 (26, 59)	57.5 (31, 66)
Range	8 to 85	8 to 85	16 to 80
% ≥ 50	39	36	60

since 1965, including those involving surface snorkelling and breath-hold diving (using some related equipment) in Australia.[6]

Earlier epidemiological reports have analyzed periodic snorkelling fatality data from 1987 to 1996[7] and 1994 to 2006.[8] The author collected all relevant coronial data for 2001 to 2013 and these are analyzed here. The aim of this study was to identify characteristics of victims of fatal snorkelling (i.e., both surface snorkelling and breath-hold diving) accidents in Australia, to identify underlying factors and risks associated with such activities and to inform appropriate countermeasures.

Methods

Ethics approval for the collection and reporting of these data was received from the Victorian Department of Justice Human Research Ethics Committee, the Royal Prince Alfred Hospital Human Research Ethics Committee, the Coronial Ethics Committee of the Coroner's Court of Western Australia, and the Queensland Office of the State Coroner.

A comprehensive search was made of the National Coronial Information System (NCIS)[9] to identify snorkelling and breath-hold diving-related cases that were reported to Australian State Coronial Services for the years 2001–2013, inclusive. These were matched with cases collected by DAN AP via the media or the diving community.

For cases prior to 2004, the author reviewed the coronial reports in conjunction with the relevant Project Stickybeak reports published in the diving medical literature.[10–12] The procedure followed for cases between 2004 and 2012 was as follows:
1. Two of the research team reviewed the police reports, witness statements and coronial reports and independently prepared a summary of each incident.
2. The author reviewed the two reports, investigated any discrepancies and prepared edited incident summaries.
3. The incident summaries, coronial and autopsy reports were independently reviewed by a research team, which variously included several diving physicians, a forensic pathologist with extensive experience in diving autopsies, a retired judge and researchers with substantial experience in diver training, data collection and accident management.
4. Annual series reports were written and published.[4,13–20]

The author solely reviewed the coronial data for cases in 2013 and extracted relevant data.

A single Poisson model provided a good fit to the deaths data across the whole study period. Analyses were performed using the Stata 15 software.[21]

Results

HISTORICAL DATA

Between 1965 and 2013 there have been a total of 337 identified deaths in snorkellers and breath-hold divers (hereinafter the combination is mainly referred to as 'snorkellers'). Figure 1 shows the annual snorkelling-related death counts with the modelled trend from the Poisson regression model. On average, snorkelling-related deaths rose by a factor of 1.55 (95% CI 1.41–1.70) each decade – so that each decade had on average 55% more deaths than the previous decade. Table 1 shows the age and gender data for this 48-year period.

Figure 2 shows the mean age at death in each year, along with the trend line fitted by the weighted least squares regression model for the years 1965 to 2013. The mean age at death rose steadily across the period to around the year 2000, when it appears to have reached a plateau.

STUDY PERIOD 2001–2013

Between 01 January 2001 and 31 December 2013, there were 175 recorded fatal incidents involving snorkellers and breath-hold divers in Australian waters. Based on the reported activity at the time of the incident, it seems reasonable to presume that 122 of the victims were predominantly 'surface snorkellers' (generally less experienced and engaged in sightseeing) and 52 were breath-hold diving (predominantly more experienced and engaged in hunting or harvesting seafood). There was insufficient information of the single remaining victim on which to make such an assessment.

Demographics

The victim demographics for this period are presented in Table 2. They were predominantly 'middle-aged' males. The age distribution for victims is shown in Figure 3. The modal class was 60–69 years and one half were aged 50 years or older. The surface snorkellers were older than the breath-hold divers with means of 53 and 39 years, respectively. The body mass indices (BMI) were available for 140 (80%) of the victims. Almost two thirds were overweight or obese, as indicated in Table 3.

Figure 1
Snorkelling and breath-hold diving fatalities in Australia, 1965–2016

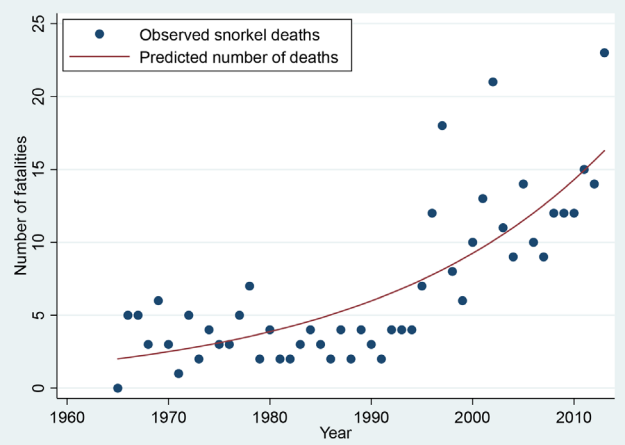


Figure 2
Mean age at death of victims of fatal snorkelling-related incidents, 1965–2013

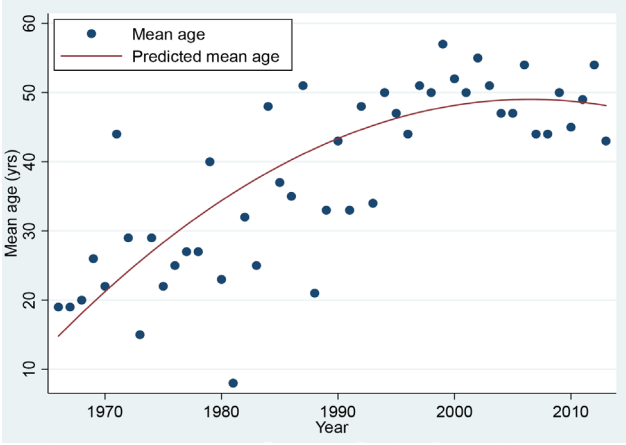


Table 2
Age measures and gender of snorkelling victims, 2001–2013

Measure	All (*n* = 175)	Male (*n* = 157)	Female (*n* = 18)
Mean (SD)	49 (18)	47.8(18.3)	59 (12.1)
Median (IQR)	51 (32, 64)	47 (31, 62)	62.5 (55, 66)
Range	15 to 85	15 to 85	25 to 70
% ≥ 50	51	45	89

Table 3
Body mass index (BMI) of victims, where known (*n* = 140). *25–29.9 kg·m^2, # ≥ 30 kg·m^2

BMI, kg·m^2	Mean (SD)
All	27 (5)
Male	27 (5)
Female	27 (7)
Overweight*	***n* (%)**
All	57 (41)
Male	54 (43)
Female	3 (21)
Obese#	***n* (%)**
All	33 (24)
Male	30 (24)
Female	6 (42)

Training and experience

There were only 23 reports (13%) indicating that the victim had some related training, and these included 22 with scuba training and one with apnoea diving training. Sixty-five victims (37%) were reported to have been experienced, 23 (13%) had some experience, 42 (24%) had no experience, and in 45 cases (26%) the victim's experience was unreported. The categories are based mainly on descriptive information from witness statements and subject to these limitations. Of the 128 snorkelling incidents where there was an indication of the victim's swimming ability, 24 were reported to have been weak or non-swimmers.

Location and setting

The distribution of the fatalities is shown in Table 4, the majority occurring in Queensland. Victims in Queensland were generally older than those in other locations. Sixty-five (37%) of the deaths occurred in a 'commercial' setting (that is, dives were organized by a professional entity such as a dive tour operator). This category included 47% of the surface snorkellers and four percent of the breath-hold divers. All but three of the deaths in a commercial setting were in Queensland and these comprised 60% (62/104) of the total deaths in Queensland. These mainly occurred during day trips involving snorkelling on the Great Barrier Reef (GBR).

Origin of victims

Eighty of the 104 (78%) snorkelling victims in Queensland were tourists, 73 from overseas and seven from interstate. Thirty percent of victims in Western Australia were tourists and there were relatively few deaths involving tourists elsewhere. Tourists snorkelling in Queensland had a mean age of 57 years and were older than tourists elsewhere (mean 54 years). More than 95% of the tourists appeared to have been predominantly surface snorkelling rather than breath-hold diving.

Buddy / Group situation

It is sometimes difficult to determine exactly when during an incident sequence that separation occurred. However, based on the information available, almost three quarters of the snorkelling victims were alone at the time of their incident.

Figure 3
Distribution of snorkel fatalities by age and gender (n = 175)

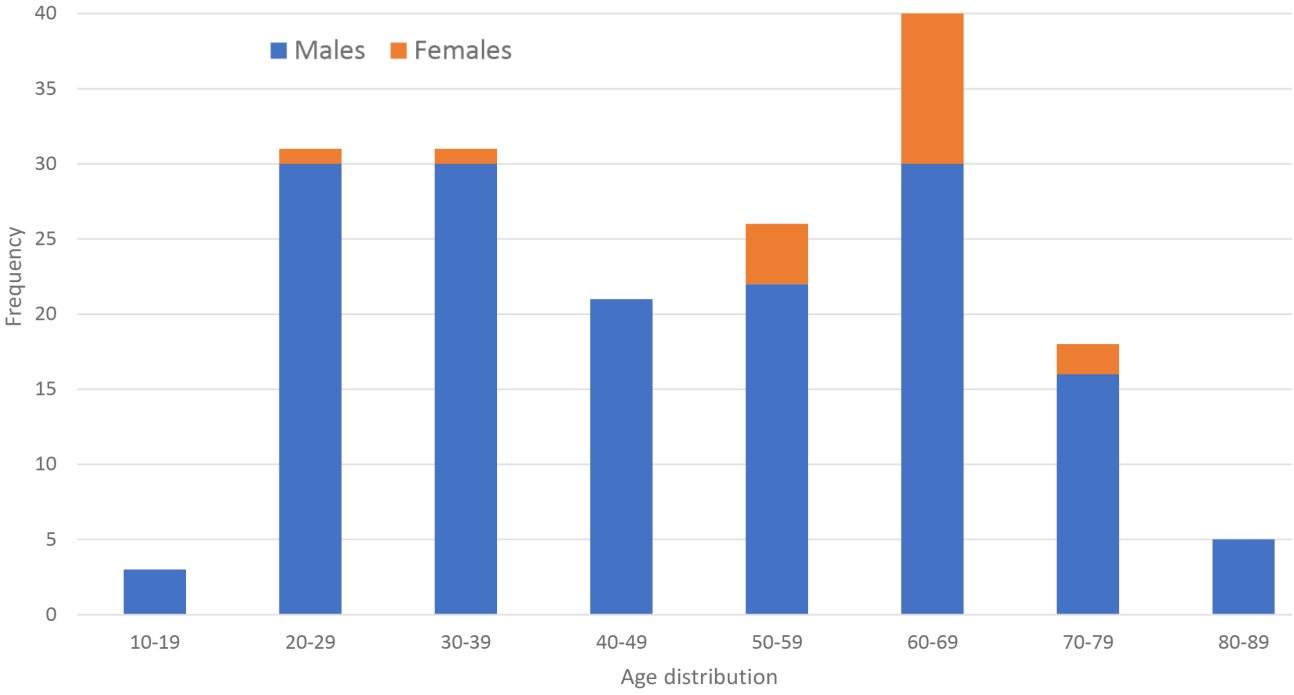


Table 4
Distribution and mean age of snorkel fatalities by State and Territory. QLD = Queensland; WA = Western Australia; NSW = New South Wales; VIC = Victoria; NT = Northern Territory; ACT = Australian Capital Territory; SA = South Australia; TAS = Tasmania

Location	*n* (%)	Age mean (SD)
QLD	104 (59)	53 (18)
WA	30 (17)	45 (17)
NSW	25 (14)	43(18)
VIC	10 (6)	34 (11)
NT	3 (2)	44 (18)
ACT	1 (1)	22
SA	1 (1)	42
TAS	1 (1)	42

Forty-seven (27%) had set out solo and 81 (46%) appeared to have separated from their buddy or buddies before the incident. Thirty-seven percent of the breath-hold divers had set out solo compared to 21% of the surface snorkellers.

Depth of incident

The vast majority (71%) of the incidents occurred at the surface. Four victims collapsed immediately after reaching the boat or land. Of the 13 incidents that were known to have occurred underwater, seven were at depths shallower than five metres, one was at 15 metres' seawater (msw) and five occurred at an unknown depth during ascent.

Weighting and floatation aids

Only 32 (18%) of the victims were known to have been wearing a weight belt and half of these were still wearing their belt when found. No specific floatation aids were used by 102 (59%) of the victims, although 14 (8%) were wearing wetsuits. Of the 17 victims who were wearing or carrying floatation aids, eight wore a life vest or jacket and seven held other floatation devices. In two cases, the type of aid was not reported.

Chain of events analysis

This chain of events analysis (CEA) is based on provisional criteria which have not been formally validated, but which have been used by the author and associates in several previous reports.[4,13,14] It utilizes similar criteria to those used (and validated) for Australian scuba diving accidents.[22]

PREDISPOSING FACTORS

Two hundred and nine predisposing factors were identified as possible or likely contributors to 173 of the fatal incidents. No factors were identified in two incidents. The main factors were health-related (n = 72) and included significant pre-existing medical conditions (n = 58), impairment by obesity (n = 4), diving whilst under the effects of drugs (n = 2). The distribution of the overall predisposing factors is shown in Table 5.

Table 5
Predisposing factors associated with 175 fatal snorkelling incidents. Some incidents involved multiple predisposing factors

72 (41%) – Health mean (SD) age 60 (15), 89% male Significant medical history: Obesity, older age	**23 (13%) Activity** mean (SD) age 30 (8), 96% male Extended apnoea (± hyperventilation) Spearfishing
53 (30%) Planning mean (SD) age 40 (16), 96% male Solo or poor buddy system Obviously unsuitable conditions	**10 (6%) Poor supervision** mean (SD) age 54 (17), 80% male Lookout failure In-water supervision failure
45 (26%) Organisational/Training/ Experience/Skills mean (SD) age 46 (18), 81% male Inexperience/poor skills Poor choice of site or conditions	**6 (3%) Equipment-related** mean (SD) age 40 (3), 100% male Weight belt problems Lack of fins and/or buoyancy aids

Table 6
The incidence of pre-existing conditions in 58 snorkellers and the associated disabling injuries in the fatal incidents. CVA = cerebrovascular accident; IHD = ischaemic heart disease; IPO = immersion pulmonary oedema; SAH = sub-arachnoid haemorrhage

Condition	*n* (%)	Disabling injury
Respiratory		
Asthma	1 (1.7)	asphyxia
Cardiac		
Arrhythmia	9 (15.5)	cardiac (8), unknown (asphyxia? IPO?, 1)
IHD (diagnosed)	22 (37.9)	cardiac (19), unknown (cardiac? asphyxia?, 3)
IHD (undiagnosed)	6 (10.3)	cardiac (5), asphyxia (1)
Valvular heart disease	3 (5.2)	cardiac (1), SAH (1), unknown (1)
Cardiomyopathy	1 (1.7)	cardiac
Other		
Drug/alcohol abuse	4 (6.9)	cardiac (3), asphyxia (1)
CVA	3 (5.2)	cardiac (3)
Diabetes	3 (5.2)	cardiac (3)
Epilepsy	3 (5.2)	asphyxia (3)
Hypertension only	3 (5.2)	cardiac (3)

Pre-existing medical conditions

Although medical histories were often unavailable, based on those available, as well as witness reports and autopsy results, pre-existing health conditions were believed to have been possible contributors in 72 (41%) of the incidents, and highly probable contributors in 58 (33%) of these. The most common condition was ischaemic heart disease (IHD), which was identified in at least 28 of the victims.

The nine pre-existing arrhythmic conditions included four atrial fibrillation, three tachycardias of unreported nature, and two other unknown arrhythmias. The predominant disabling injury in those with an identified pre-existing cardiac, cardiovascular or cerebrovascular condition or diabetes was cardiac-related (40/47 cases).

One asthmatic snorkeller died as a direct result of his asthma. Three snorkellers with known epilepsy drowned in unwitnessed circumstances. Although unproven, epilepsy may have been a contributor to some, or all, of these incidents. Table 6 shows the pre-existing conditions in 58 snorkellers where these conditions were likely to have been contributory.

Medications

The medications taken by 50 of the victims were known, although nine others were reported to have been taking unknown medications. It is likely that some others were also taking medications, but this information was not gathered. The medications will be the subject of a future report.

Planning

The main potentially contributory planning-related issue was snorkelling solo ($n = 18$) or with a very loose or absent buddy system ($n = 12$). Five victims were practicing extended breath-holding while alone in a pool. In 12 cases, the victims set out in conditions that were obviously unsuitable. Three

Table 7
Triggers associated with 175 fatal snorkelling incidents. Some incidents involved multiple triggers

98 (56%) Environment-related mean (SD) age 56 (16), 92% male conditions immersion effects marine animal and boat contact	**14 (8%) Exertion-related** mean (SD) age 60 (13), 93% male non-conditions-related carrying equipment and catches surface swims
27 (17%) Unknown mean (SD) age 46 (17), 85% male	**6 (3%) Anxiety-related** mean (SD) age 55 (16), 83% male
22 (13%) Extended apnoea mean (SD) age 28 (6), 95% male spearfishing practicing in pool or ocean	**4 (2%) Primary error** mean (SD) age 53 (15), 100% male entanglement
18 (10%) Water aspiration mean (SD) age 56 (16), 67% male primary aspiration	**3 (2%) Equipment-related** mean (SD) age 33 (18), 100% male entanglement in speargun cords tight wetsuit inappropriate snorkel

of the victims were snorkelling in an area with known boat traffic without displaying a 'Diver Below' flag and were subsequently hit by boats.

Organisational / experience / skills

The vast majority of these cases were related to the inexperience of the victims who were often first-time snorkellers. Organisational failures included poor selection or demarcation of the snorkelling site, the decision to allow snorkelling in adverse conditions, inadequate numbers or training of lookouts, and poor maintenance or absence of suitable first aid equipment. One failure included a member of staff giving poor advice about the potential seriousness and implications of an individual's medical condition.

Activity

There were 26 incidents (15%) which involved activities with a likely increased risk of a mishap. Twenty-two of these involved breath-hold divers who were pushing their apnoea limits while spearfishing, or for practice, and appeared to have drowned as a result of apnoeic hypoxia. Five of these were noted to practice pre-dive hyperventilation, although it is likely that more had done so.

Poor supervision

These incidents included four cases where there was an obvious failure of the lookouts in a commercial setting. The other cases involved poor supervision in the water by guides and in two cases spearfishing buddies who broke their agreed protocol of 'one-up-one-down', with severe consequences.

Absence of appropriate equipment or use of obviously faulty equipment

These incidents mainly involved the absence of quick-release buckles on weight belts, over-weighting, and not using fins in strong currents. There were also multiple incidents where the use of buoyancy aids may have prevented problems in weak swimmers.

TRIGGERS

One hundred and ninety-two possible or likely triggers were identified in 148 of the fatal incidents. No triggers were identified in 27 of the incidents and multiple possible triggers in 44. The frequencies and proportions of the various trigger categories are shown in Table 7.

Environmental

These triggers were often associated with adverse conditions (n = 36), namely strong currents (16), rough seas (13), or both (7). Forty-eight deaths (27%) were believed likely to have been associated with the effects of immersion; half in combination with other factors such as exertion or aspiration, and half to immersion *per se*. Almost all the latter were, by definition, associated with in cardiac disabling injuries. It was suspected that two events were likely to have been associated with epilepsy precipitated by sensory effects of immersion.

Eight incidents involved interaction with a marine creature, three of which were sharks, two Irukandji jellyfish, two crocodiles and one stingray. Four incidents involved impact with a boat and two snorkellers became entangled in lines.

Extended apnoea

These incidents involved breath-hold divers who appeared to have become unconscious as a result of extended apnoea, with or without pre-dive hyperventilation. Eleven of these were spearfishing, five were practicing extended breath-holding in the ocean, and five drowned while practicing

Table 8
Disabling agents associated with 175 fatal snorkelling incidents

78 (45%) Medical mean (SD) age 59 (15), 91% male ischaemic heart disease pre-existing arrhythmia cardiac abnormality subarachnoid haemorrhage	**20 (12%) Unconsciousness (laryngospasm?)** mean (SD) age 46 (19), 75% male
23 (13%) Environmental mean (SD) age 41 (14), 100% male adverse conditions marine animal/boat injury entrapment	**9 (5%) Buoyancy** mean (SD) age 37 (14), 100% male
21 (12%) Apnoeic hypoxia mean (SD) age 28 (5), 95% male	**24 (14%) Unknown** mean (SD) age 47 (16), 88% male

Table 9
Disabling injuries associated with 175 snorkelling fatalities. CVA = cerebrovascular accident; F = female; IPO = immersion pulmonary oedema; M = male; SAH = subarachnoid haemorrhage

Disabling injury	*n* (%)	M (%)	F (%)	Age mean (SD)	Age M mean (SD)	Age F mean (SD)
Asphyxia	70 (40)	91	9	39 (16)	37 (15)	59 (13)
Cardiac	61 (35)	90	10	61 (13)	62 (13)	59 (6)
Trauma	10 (6)	100	0	40 (11)	40 (11)	– (–)
IPO	1 (0.6)	0	100	61 (–)	– (–)	61 (–)
CVA	2 (1.2)	100	0	52 (–)	52 (–)	– (–)
SAH	1 (0.6)	100	0	52 (8)	52 (8)	– (–)
Uncertain	30 (17)	83	17	49 (20)	47 (20)	58 (19)

extended apnoea alone in a swimming pool. All but one of this cohort were relatively young males.

Aspiration

Although there were possibly many more, based on witness reports there were 18 incidents (10%) in which the primary trigger appeared to have been water aspiration, most likely through the snorkel, by inexperienced snorkellers in good conditions.

Exertion

Exertion, unrelated to adverse conditions, appeared to have been a trigger in 14 incidents (8%). Ten of these resulted in a cardiac-related disabling injury and two in cerebrovascular events.

Anxiety

Anxiety is likely a trigger in many deaths of inexperienced snorkellers. However, it was only included as a factor in this analysis when there were specific witness accounts reporting that the victim displayed signs of anxiety. There were only six such accounts (3%), all involving novices.

Equipment

Two of these incidents involved spear fishers who became entangled in their lines, another incident was triggered by difficulties associated with a tight wetsuit, and one by the victim breathing what likely became a hypercapnoeic and hypoxic gas through a hose rather than a snorkel.

Primary error

Although many incidents involved errors by snorkellers along the chain of events, these were particularly obvious in three cases, all of which involved experienced snorkellers becoming entangled in lines.

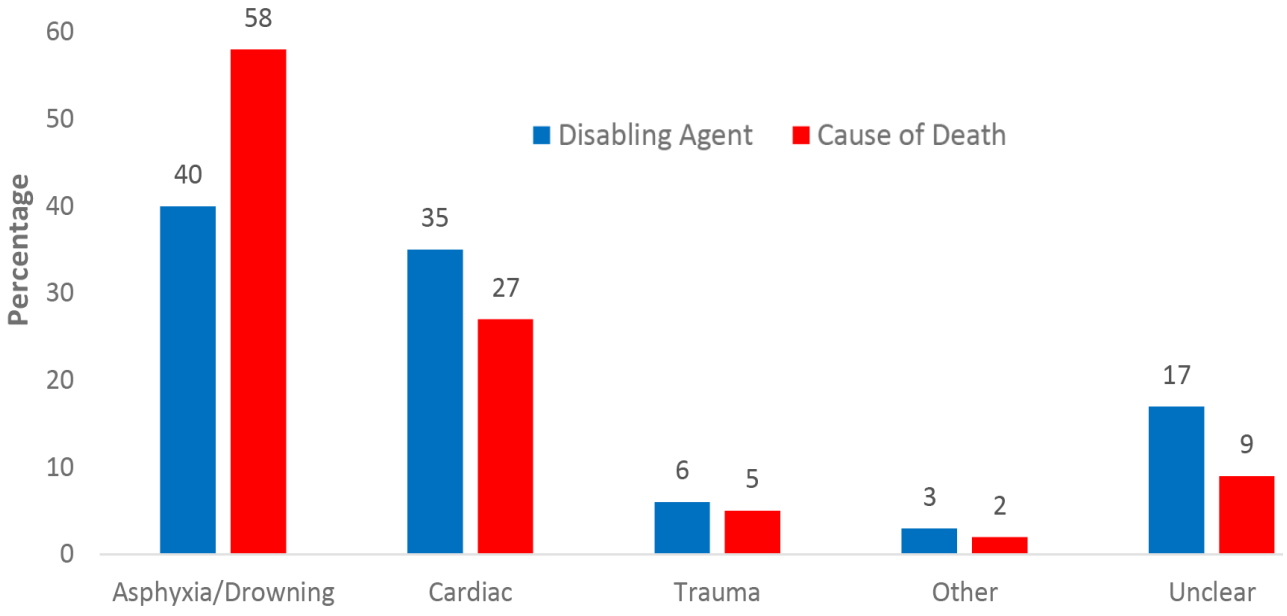
DISABLING AGENTS

There were 151 likely disabling agents identified in the 175 incidents, as shown in Table 8.

Medical

Of the 78 medical-related disabling agents, 63 appear to have been associated with pre-existing cardiac-conditions (some occult), predominantly cardiovascular/ischaemic heart disease. These included nine incidents where there

Figure 4
Comparison of disabling agents and causes of death in 175 snorkelling fatalities



was autopsy evidence of myocardial infarction. Five victims were believed to have been disabled by their pre-existing arrhythmic conditions.

Environmental

These included injuries from marine animals, which included sharks (3), crocodiles (2), irukandji-causing jellyfish (2) and a stingray. Six snorkellers were disabled by adverse sea conditions and three by contact with a boat.

Apnoeic hypoxia

The disabling agent in another 21 deaths was likely to have been a hypoxic blackout before, during or immediately after ascent as a result of extended apnoea.

Loss of consciousness post aspiration

Loss of consciousness secondary to water aspiration is likely to be a relatively common disabling agent in snorkelling accidents. There were 12 incidents identified, all involving inexperienced snorkellers, where there appeared to be no other likely extenuating factors and it is probable that the victim aspirated water (generally through the snorkel) in calm conditions and became unconscious, possibly as a result of laryngospasm. The remainder appear involve water aspiration secondary to some triggers, which in most cases involved challenging sea conditions for inexperienced snorkellers.

Buoyancy

Five of the victims were poor swimmers and two of these were wearing street clothes without fins. In three cases, the victims carried too much weight on their weight belts and were disabled as a result, one subsequent to becoming entangled in a line.

DISABLING INJURIES

The predominant disabling injuries identified were asphyxia (40%), cardiac causes (35%), although another 15 incidents (9%) may have involved cardiac-related disabling injuries. The relative occurrence is shown in Table 9. At least 45% of the snorkelling-related deaths in Queensland were cardiac-related, compared with 30% in Western Australia and 20% in New South Wales. There were no deaths identified as cardiac-related in the other States or Territories. There was only one death attributed to immersion pulmonary odema (IPO). However, due to the difficulty of distinguishing IPO from drowning at autopsy, it is possible that there were others.

A cardiac disabling injury was most often associated with exertion as at least one of the triggers [OR 5.79 (2.73, 12.30), $P < 0.0001$]. There were no other significant associations.

CAUSES OF DEATH (COD)

The predominant causes of death identified were drowning (58%), cardiac (27%) and trauma (8%). Figure 4 compares the likely disabling agents as identified by COE analysis with

the causes of death reported by the pathologists. Drowning has been the default finding in the absence of other obvious causes. The difference between the 58% drowning as COD and 40% asphyxia as disabling injury may reflect cases where drowning was secondary to a medical condition, such as a cardiac arrhythmia of which there is no direct evidence at autopsy.

Discussion

The number of snorkelling-related fatalities in Australian waters increased by approximately 50% for each decade from 1965 to 2013, likely as a result of increased participation, particularly of older individuals. One hundred and seventy-five such deaths occurred between 01 January 2001 to 31 December 2013. Most of the victims were middle-aged males, many of who were international tourists snorkelling in Queensland. Asphyxia was likely the disabling injury in 40% of these incidents, and another third of the victims appear to have been disabled by a cardiac-related event. It is important to carefully analyze these incidents in order to develop and refine appropriate countermeasures.

Demographics and characteristics

The age of the victims has increased over time, reaching a mean of 49 years during the study period, with half of these being at least 50 years old. The proportion of female victims also increased, although still over 90% of deaths were in males.

Sixty-five percent of the victims were overweight or obese. There is an association between the presence of significant health conditions and being overweight or obese,[23–26] as well as an association between obesity and sudden cardiac death.[27,28] Of particular relevance, the likelihood of a cardiac event may be increased in the context of immersion and this may partly explain the increasing incidence of cardiac-related death associated with aquatic activities.[29–31]

It is unsurprising that the majority of the victims were in Queensland and that these were generally older than in other locations. Most were international tourists and inexperienced snorkellers, who had likely included snorkelling on the GBR on their 'bucket list'. Diving-related tourism is an important income source for Queensland and there is a plethora of commercial snorkelling operations catering to the vast number of participants. These operators are required to comply with a regulated code of practice (COP)[32] in an attempt to minimize the associated morbidity and mortality, and to avoid adverse publicity associated with such deaths. Although codes of practice have been created for Victoria[33] and WA,[34] these are voluntary, weaker, likely unknown to many operators and are often not followed. Many incidents in places other than northern Queensland involved locals, with some or considerable snorkelling experience. Increased tourist and snorkelling activity along the Kimberley Coast likely accounts for the rising number of incidents in Western Australia, most involving non-locals.

Until the relatively recent introduction of formal training and certification in apnoea diving, very few snorkellers were trained, other than when undertaking scuba diving certification. Coronial reports on snorkelling fatalities rarely provide an accurate depiction of the level of experience of the victims. The inclusion of such information would be valuable in better targeting appropriate countermeasures, such as increased skills training, orientation and supervision.

Similarly, swimming ability was often not recorded. At least 15% of victims were known to be weak or non-swimmers but the actual proportion is likely to have been substantially higher. However, even strong swimmers may have difficulty snorkelling unless they have enough opportunity to learn the required skills. A suitable floatation device can help the tired, weak or non-swimmer to stay afloat and should be encouraged. However, participants are often reluctant to use these for various reasons. A lifejacket, vest or wetsuit usually needs to be well-fitted in order to be effective. The use of well-fitting fins is strongly recommended, especially in a strong current.

Health-related issues

The CEA highlights the importance of the addition of the link for predisposing factors, with the identification of more than 200 factors that were present prior to the excursion and which likely, or possibly, contributed to these deaths. Human factors may be influential throughout much of the accident chain. These include pre-existing health conditions, poor fitness, lack of experience, organisational shortfalls and poor planning or supervision. In addition, inattention, carelessness, inappropriate attitude, poor decision-making and inappropriate actions, whether prior to or during an incident, can all influence the chain of events and outcome.

Over 40% of the predisposing factors identified were health-related, unsurprising considering the mature age of much of the snorkelling cohort, particularly the surface snorkellers. Many had pre-existing medical conditions, often cardiac-related, whether diagnosed and treated, or occult. Based on witness reports and evidence of cardiac disease or abnormality at autopsy, many of the deaths thought to have been cardiac-related have been attributed to arrhythmias.[4,13–20] However, in the absence of a definitive post-mortem test and a lack of cardiac monitoring at the time of the incident, this remains speculative and warrants further investigation. While the physiological effects of immersion are well understood in the healthy individual, few data are available on immersed exercise in the more elderly who, in addition to often having underlying cardiovascular pathology and limited exercise capacity, may well be on medication that may modify their ability to deal with the physiological challenges involved.

It is important for commercial snorkel operators to explain the risks that certain medical conditions can pose while snorkelling, albeit avoiding offering medical advice unless medically qualified. It is also necessary for participants to truthfully declare such conditions so that suitable risk management measures can be enacted. This health message should also be relayed to individuals through clubs and media, to raise awareness as the opportunity arises.

Poor planning

Planning-related issues also played a large part in many of the incidents, the major one being the lack of an effective buddy system. As with scuba diving, the close proximity of a vigilant buddy can be lifesaving in the event of a mishap. Even if an inexperienced buddy is unable to perform a rescue, they may be able to alert others and so reduce the time to rescue. The fact that three quarters of these victims were alone at the time of the incident highlights the on-going need to reinforce this message, and for snorkellers to act accordingly. This should be an integral part of the preparation and briefing in a commercial setting.

The breath-hold divers were more likely to set out alone and in an unsupervised setting. Even highly experienced breath-hold divers can benefit from close supervision and the one-up-one-down protocol should be encouraged and followed.

Prompt identification of a distressed or unconscious snorkeller, together with rapid rescue will maximise the chances of survival. However, it is common for there to be substantial delays in recognition as it can sometimes be difficult to determine whether a motionless snorkeller is unconscious. This is particularly a problem with a large group of snorkellers, such as in a commercial setting. It is obvious that ratios should be minimised to increase safety, although commercial imperatives often prevail. Professional lookouts should be well-trained in scanning techniques. They should have a low tolerance to investigate if an individual is in distress. In addition, suitable rescue techniques need to be identified and practiced ensuring that they can be done swiftly and effectively when needed. First aid-related equipment (e.g., automated external defibrillator and suitable oxygen unit) needs to be readily accessible and operational, with appropriately trained staff available.

Experience, skills and conditions

As indicated earlier, most of the surface snorkelling victims were inexperienced and often first-time snorkellers. Frequently, such individuals are given only a very basic briefing and orientation. Where possible, this should be extended until the participants can demonstrate reasonable competence in the use of the mask, snorkel and fins. The level of supervision needs to be adjusted to match their skills and apparent health and fitness. The relevant COP in Queensland was recently adjusted to encourage this.[32]

On the other hand, in this series as indeed in earlier reports,[7,8] there was a significant cohort of, mainly very experienced, breath-hold divers who appear to have succumbed to apnoeic hypoxia. Some of these were reported to have practiced pre-dive hyperventilation. However, this information is often not included in witness statements and police investigators are encouraged to specifically probe this to better inform the extent of the problem. Many breath-hold divers believe that they cannot blackout without hyperventilation, but this is untrue. Due care must be taken with extended apnoea and close supervision is always prudent, although often not practiced.

It is always important to carefully consider prevailing and predicted conditions before entering the water. Conditions must be matched with each individual's skills and experience.

Boats and marine animals

Four of the deaths involved individuals who were struck by boats while snorkelling. It is always prudent to display a Diver Below flag, especially in areas frequented by boats.

Two of the three shark attack victims and one of those attacked by a crocodile were spearfishing at the time of the attack, an activity associated with an increased risk.[35] Spear fishers are well-advised to select a dive site which is not known to be frequented by large sharks, and to keep their catch well away from them to reduce the likelihood of such an incident. The wearing of protective clothing, such as a stinger suit, will greatly reduce the likelihood of an Irukandji sting.

Limitations

As with any uncontrolled case series, the collection and analysis of the fatality data are subject to inevitable limitations and uncertainties associated with the investigations. These include:

- Incomplete case data: Deaths were sometimes unwitnessed and, therefore, potentially important observational information was missing. Witness reports varied in their likely reliability. Police reports varied in their content, often related to the expertise of the investigators. This may lead to incomplete or inaccurate chain of events analyses.
- Autopsy reports: These can sometimes be unreliable as a result of the inability to detect direct evidence of cardiac arrhythmias; among other factors.
- Even with the use of a template, classification of cases into a sequence of five events using chain of events analysis is imperfect and remains vulnerable to some subjectivity.

Conclusions

Various human factors can play a substantial role throughout

the chain of events leading to a snorkelling fatality. These include pre-existing health conditions, poor skills, inexperience, poor fitness, organisational shortfalls, poor planning or supervision, among others. Each factor can predispose a diver to an incident or exacerbate a problem once adverse circumstances develop.

Chronic health conditions, such as ischaemic heart disease and cardiac arrhythmias, likely played a major role in up to 40% of these deaths, with one third attributed to a cardiac disabling injury. The interplay of immersion, exertion, anxiety, aspiration and temperature can precipitate an arrhythmia or a coronary event in a susceptible individual, which, in the water will often be fatal. It is, therefore, increasingly important to educate the community, doctors and dive industry professionals about the very real potential problems associated with the interaction between certain health-related conditions, especially cardiovascular conditions, and snorkelling.

Close supervision is strongly recommended for inexperienced snorkellers due to their likely poor skills, as well as for experienced breath-hold divers due to the potential for apnoeic hypoxia. Conditions should be matched with each participant's skills and experience. The use of a diver below flag and careful site selection can reduce the likelihood of injury from a boat, or adverse interaction with a marine predator.

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Conflict of interest and funding

John Lippmann is the Founder and Chairman of DAN Asia Pacific. DAN is involved in the collection and reporting of dive accident data and provides evacuation cover and dive injury insurance to recreational divers. This study was funded by DAN Asia Pacific and the Australasian Diving Safety Foundation (ADSF).

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Descriptive study of diving injuries in the Canary Islands from 2008 to 2017

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Key words
Diving incidents; Epidemiology; Scuba diving; First aid; Hyperbaric oxygen therapy; Tourism

Abstract
(Guillén-Pino F, Morera-Fumero A, Henry-Benítez M, Alonso-Lasheras E, Abreu-González P, Medina-Arana V. Descriptive study of diving injuries in the Canary Islands from 2008 to 2017. Diving and Hyperbaric Medicine. 2019 September 30;49(3):204–208. doi: 10.28920/dhm49.3.204-208. PMID: 31523795.)
Introduction: This research reports the epidemiology of diving injuries managed in the Hyperbaric Medicine Unit of the Canary Islands University Hospital.
Methods: Data were extracted from the clinical records of all divers injured and admitted to the unit for treatment of dysbaric diving injuries between 2008 and 2017, inclusive.
Results: One-hundred and thirty diving injuries were recorded. Most (71%) occurred in men and 43% were foreigners. Eighteen per cent either had no diving certification or that information was not recorded in the clinical chart. Only a third of the 40% of divers who had some form of on-site first aid treatment received oxygen and oral rehydration. Type 1 decompression sickness (DCS) was diagnosed in 56 divers (43%) and Type 2 in 67 (52%), whilst seven were treated for omitted decompression. At discharge, 122 (94%) were asymptomatic, whilst 5% experienced some residual sensory or other changes. One diver who presented late remained quadriparetic and one, admitted in a state of coma, died. Only 76% of the injured divers had specific diving accident insurance and, of those, 58% were foreign divers.
Conclusions: Over half of the injured divers did not receive any on-site first aid. The majority (94%) of treated injured divers were discharged without sequelae. Based on these data, several public health recommendations for the Canary Islands are made.

Introduction

Hyperbaric oxygen treatment (HBOT) has a number of indications that may be divided into established, experimental and unestablished.[1–4] Amongst the established indications are decompression sickness (DCS) and arterial gas embolism (AGE) secondary to pulmonary barotrauma, collectively termed decompression illness (DCI). These conditions can affect all divers whether professional or not. HBOT is the gold standard treatment for these conditions.[2,4]

The Canary Islands, located in the Atlantic Ocean between latitudes 29º24'40" N and 27º38'16" N and longitudes 13º19'54" W and 18º09'38" W, form an archipelago of Macaronesia. The islands are of volcanic origin, consisting of eight major inhabited islands (Tenerife, La Palma, La Gomera, El Hierro, Gran Canaria, Lanzarote, Fuerteventura and La Graciosa) and five smaller islets. A coastline of over 1,500 kilometres, the existence of pleasant, spring-like temperatures throughout the year and clear waters makes them an excellent open-water dive site.[5] The main economy is tourism, with approximately 15 million visitors annually. A large number of these visitors wish to dive, so require adequate staff and facilities.[6,7] In Tenerife, there is a Hyperbaric Medicine Unit (HMU) with a hyperbaric chamber linked to the Canary Islands University Hospital (acronym in Spanish, HUC) that provides care for diving injuries that may occur throughout the whole of Macaronesia.

According to international statistics, the number of diving injuries in proportion to the number of dives and divers is very low when compared to the morbidity of other sports

Table 1
Diving injury locations in the Canary Islands over a decade, 2008 to 2017

Location	Number	Percentage
Tenerife	92	71
Gran Canaria	16	12
El Hierro	9	7
La Palma	5	4
Other	4	6
Total	130	100

activities.[8–10] However, although of low incidence, 35% of diving injuries are severe and 5–10% may be life-threatening.[10,11] The objectives of this paper were to report the nature of the diving injuries that have been treated at the HMU and their outcome at discharge.

Methods

This was a retrospective review carried out in accordance with the Helsinki Declaration and approved by the Human Ethics Committee of the Canary Islands University Hospital (2017_15 EPIBUCAN01).

Admission for treatment of a diving injury to the HUC was the only selection criterion applied. The data were extracted from the HMU's clinical records, transcribed to a standard form and then entered into a Microsoft Excel® database. The medical records of all patients admitted to the HMU between May 2008 and December 2017 were reviewed. This period was chosen because a new modern chamber was installed in May 2008, and patient records prior to this date were insufficient for review.

From this data base, only those patients diagnosed with dysbaric injuries were extracted and the following data recorded for each case: age; gender; nationality; date of the diving accident; date of arrival at the UHC Emergency Service; type of diving activity; diver certification; diving accident insurance; diving incident location; type of dive; DCS type; maximum depth; total dive time; latency between last dive and symptom onset; on-site first aid measures; means of transport used; type of treatment administered; recovery status at discharge.

Traditionally, DCI has been classified into DCS Type 1 (DCS with cutaneous symptoms, 'bends' or musculoskeletal pain and lymphatic system symptoms), DCS Type 2 (DCS with neurological, cardiovascular, pulmonary or inner ear involvement) and AGE.[12] In our study we found that DCI was classified in the clinical records only into DCS Type 1 and DCS Type 2.

Table 2
Means of transport used in the Canary Islands to evacuate injured divers to the recompression chamber on Tenerife

Mode of transport	Number	Percentage
Own means	50	38
Ambulance	35	27
Helicopter/fixed wing	34	26
No data	11	9
Total	130	100

The statistical package SPSS v.23 was used to produce simple descriptive statistics.

Results

The study includes 130 divers with dysbaric injuries. The number of diving injuries ranged from six in 2010 to 23 in 2017, with an obvious increase over the last four years (Figure 1). Seventy-one per cent were male and 29% female; median age was 38 years (range 17–70 years). Local divers comprised 57% of the sample while 43% were foreigners, with some variability in the ratio from year to year. Table 1 shows the number of incidents in various Canary Islands locations.

In relation to diving activity, 26 (20%) of incidents involved professional divers and 104 (80%) involved recreational divers. Surprisingly only 82% of the subjects had a diving certificate, either professional or recreational, the remaining 18% either having no certificate or no data existed in the clinical record. Only 76% had specific diving accident insurance and, of these, roughly half were locals and half foreign divers.

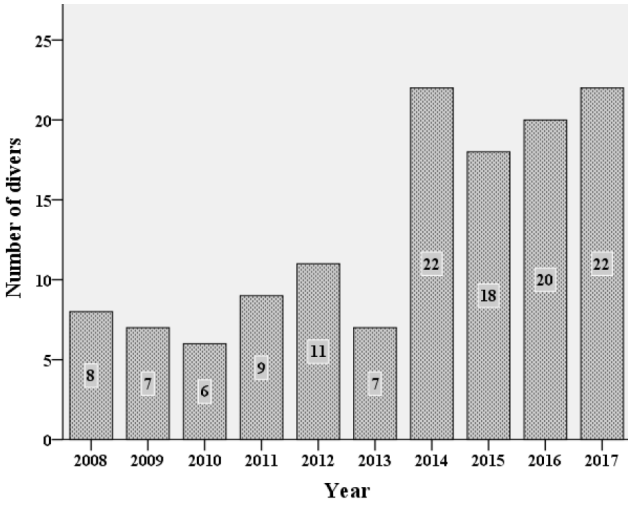
With respect to the type of diving being undertaken, 90 (69%) followed a single dive and 33 (25%) followed repetitive dives. Other types of diving included two divers following multiple breath-hold dives. On-site first aid was provided to 40%; 47% did not receive first aid and data were missing for the remainder (13%). Only normobaric O_2 was given to 24 divers (18%), normobaric O_2 and fluids (oral or intravenous) to 17 (13%) and other measures to seven. Injured divers were transported to the HUC in various ways: by their own means (50, 38%; 48 in Tenerife); by ambulance (35, 27%; 33 in Tenerife), or by helicopter or fixed wing aeroplane (34, 26%), with no data recorded for the remaining 11 (see Table 2).

The diagnoses presented in the clinical charts were Type 1 DCS in 56 divers (43%) and Type 2 DCS in 67 (52%) whilst seven presented following omitted decompression without symptoms. Treatment at HUC was observation

Table 3
Initial hyperbaric treatments administered in relation to the clinical diagnosis; USN TT5 – US Navy Treatment Table 5; USN TT6 – US Navy Treatment Table 6; the 243 kPa/60 min table was used for delayed referrals

Diagnosis	Initial hyperbaric oxygen treatment				
	USN TT5	USN TT6	243 kPa/ 60 min	Observation	Total
DCS Type 1	44	1	2	9	56
DCS Type 2	15	47	4	1	67
Omitted decompression	3	0	0	4	7
Total	62	48	6	14	130

Figure 1
Number of reported diving injuries in the Canary Islands by year



or HBOT. Observation was carried out with normobaric oxygen and fluid therapy. Initial HBOT for DCS was a United States Navy Treatment Table 5 (USN TT5) or Table 6 (USN TT6). The choices of treatment for the various diagnostic categories are shown in Table 3.

If symptoms and/or signs of the dysbaric pathology persisted once initial HBOT was completed, the diver was admitted to hospital. Additional HBOT was given over the following days (one per day), consisting of 60 minutes of HBOT at 243 kPa, with a five-minute air break after 30 minutes of treatment and a decompression time of seven minutes. These additional sessions were conducted with the diver joining other patients undergoing elective HBOT for other pathologies. Forty-three patients (33%) were treated with extra HBOT either until they were symptom-free or their condition had stabilised, (median 5, range 1 to 13). Furthermore, six patients diagnosed as 'non-acute DCS' were also treated on these 243 kPa HBOT sessions.

At discharge from the HUC, 122 of 130 divers (94%) were asymptomatic and six (5%) experienced some residual sensory or other changes. In addition, one diver injured at Cabo Verde took several weeks to present for HBOT and remained quadriparetic, whilst another, an American diver injured at Lanzarote, was admitted in a state of coma and died.

Discussion

It is important to know the epidemiology of diving injuries for a variety of reasons, such as to establish guidelines for injury prevention in divers and to develop effective public health strategies. From a public health viewpoint, there has been a large increase in the number of diving injuries in the Canaries from 2014 onwards compared to previous years (Figure 1). This requires a major study in order to establish the main contributing factors and to mitigate identified risk factors. It is possible that it simply reflects the increasing diving activity in the Canary Islands, but this is unknown.

Over 90% of the injured divers treated at the HUC were aged 25 to 64 years or more. This differs from data reported by the Divers Alert Network (DAN) in its Annual Diving Report, 2012–2015, which reports only 62% in this range.[8] It needs to be established whether this reflects a real difference from the international data. The gender distribution in this study (71% men, 29% women), is similar to that from other studies – 72% male; 28% female in one,[8] and 81% male, 19% female in another.[11] It is important to point out the high proportion (43%) of foreign divers present in our study. This likely reflects the Canary Islands as a very popular tourist destination, surrounded by sea and with many possibilities for the pursuit of recreational diving (with and without scuba).

Another important observation is that almost a quarter of the injured divers did not appear to have a diving certificate. These data are similar to those obtained by others (18% for no certification, training or unknown).[11] Lack of diving experience and knowledge could be behind many of the diving incidents. Likewise, less than half of the foreign divers had diving accident insurance; one could assume that insurance cover is not regarded as important by these divers.

The low rate of provision of on-site first aid amongst this cadre of divers is of equal concern. Some of this may reflect the latency of onset of symptoms; only 68 individuals (52%) reported symptom onset before 40 minutes post dive, by which time they may have been separated from potential first-aid providers. The failure to provide on-site first aid may also reflect a lack of appropriate equipment or reluctance to use it. This seems likely since only 13% of injured divers who received some on-site assistance, actually received the first aid recommended in relevant guidelines.[8,13] Three injured divers received in-water recompression with air as the initial treatment gas, a practice that is discouraged strongly in our environment.[13,14] Enhancing knowledge about first-aid procedures when a diving incident occurs and its impact regarding diver outcome is needed in the Canaries.

Although there are similar-sized populations in Gran Canaria and Tenerife,[15] only 12% of the diver referrals were from Gran Canaria. It is possible that a greater number of accidents may have occurred in Gran Canaria but were not referred to Tenerife, where the only hyperbaric facility is situated, because of logistical difficulties with inter-island transfer. Almost half of the divers (48%) on the island of Tenerife arrived at the HUC by their own means. In contrast, most of the injured divers from other islands came by helicopter. Air transport is the most efficient and timely means of transferring injured divers between islands. The situation of the Canary Islands as a fragmented territory of many islands with diving activities distributed over a wide area necessitates the development in the future of transportation protocols for injured divers.

Finally, we suspect that some cases in our study e.g., the American diver injured in Lanzarote admitted in a state of coma, might be AGE. The difficulty to tell the difference between DCS Type 2 (DCS with neurological involvement) and AGE, could be behind this misclassification.[12,16,17]

This study has some weaknesses that should be acknowledged. In particular, there were a variety of missing clinical and other data. Also, no post-hospital discharge outcomes were evaluated.

The following public health and clinical management recommendations are made, based on these data and their analysis:

- establishment of a central registry of diving accidents;
- improved training in and use of appropriate first-aid procedures for diving injuries;
- improved clinical documentation;
- post-discharge follow-up of the HBO-treated divers;
- development of an evacuation protocol for diving accidents for the Canary Islands in order to accelerate the transportation to the HUC hyperbaric chamber.

Conclusions

Decompression illness was more common in men than women, with nearly half the injured divers being foreigners. About a quarter appeared to have no diving certificate or no relevant data existed on their clinical record, and a similar proportion did not carry specific diving accident insurance (almost half of the foreigner divers). Two thirds did not receive any on-site first aid or no data on this was available on their clinical record. Because the hyperbaric chamber is located on Tenerife, diving injuries that occurred in other islands may have been under-reported. Over 90% of the injured divers treated were discharged without sequelae. In fragmented territories like the Canary Islands, it is desirable to have an evacuation protocol for injured divers, based on air transport (helicopter preferably).

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Review articles

Evidence for simulation-based education in hyperbaric medicine: A systematic review

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Key words
Hyperbaric oxygen; Education; Systematic review; Performance; Safety

Abstract
(Boet S, Cheng-Boivin O, Martin L, Hurskainen T, Etherington C. Evidence for simulation-based education in hyperbaric medicine: A systematic review. Diving and Hyperbaric Medicine. 2019 September 30;49(3):209–215. doi: 10.28920/dhm49.3.209-215. PMID: 31523796.)
Introduction: Evidence from many areas of healthcare suggests that skills learned during simulation transfer to clinical settings; however, this has not yet been investigated in hyperbaric medicine. This systematic review aimed to identify, summarize, and assess the impact of simulation-based education in hyperbaric medicine.
Methods: Eligible studies investigated the effect of simulation-based education for learning in hyperbaric medicine, used any design, and were published in English in a peer-reviewed journal. Learning outcomes across all Kirkpatrick levels were included. MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials were searched. Pairs of independent reviewers assessed references for study eligibility.
Results: We found no article assessing the impact of simulation-based education in hyperbaric medicine published in English. Only one potentially relevant paper published in German was found.
Conclusions: More research is needed to determine how the hyperbaric medicine community and their patients may benefit from simulation-based education to optimize both practice and patient care.

Introduction

Simulation-based education is effective for teaching technical and non-technical skills to both individuals and teams across many specialties, particularly in acute care.[1–4] Since simulation poses no risk to actual patients,[1,5] it is used across the continuum of education from undergraduate and postgraduate training to continuing professional development. Evidence suggests that skills learned during simulation transfer to clinical settings, improve team performance,[3] and in turn may improve patient outcomes.[6]

Hyperbaric oxygen therapy (HBOT) is widely used across the world to treat patients of all ages with urgent and non-urgent conditions.[7–14] Effective medical management of HBOT requires both individual and team-level clinical competencies, especially in emergency situations or when complications occur.[15] For example, HBOT can involve safety events such as hyperbaric chamber fires, acute respiratory failure or seizure, and complex cases such as patients who are mechanically ventilated.[16] Healthcare providers involved in the provision of HBOT must therefore master technical and non-technical skills, including interprofessional collaboration, for effective teamwork.

In many countries, training to be a certified hyperbaric healthcare professional currently only includes didactic lectures.[15] Training for the initial certification does not routinely involve simulation-based education and there is no formally recognized simulation course tailored to hyperbaric medicine. Based on the evidence supporting the impact of simulation practice in other areas of healthcare,[3,6] we hypothesize that a simulation-based curriculum in hyperbaric medicine may improve provider performance at both the individual and team levels, and may also benefit patients. Before we can develop a simulation-based education curriculum, it is necessary to conduct a systematic review of the evidence for using simulation-based education in hyperbaric medicine. This has not yet been done but is an important starting point for future curriculum development.

This systematic review aimed to identify, summarize

Table 1
Classification of learning outcomes according to Kirkpatrick (modified by Phillips, 1997[19])

Outcome level	Descriptor
Level 1: Reaction	Participants' view on the learning experience
Level 2a: Modification of attitudes	Changes in attitudes towards hyperbaric medicine technical and non-technical skills
Level 2b: Acquisition of knowledge and skills	Changes in technical/non-technical skill or knowledge or skill performance
Level 3: Behavioural change	Transfer of technical/non-technical learning to the practice setting
Level 4: Benefits to patients	Improvement in patient health or well-being
Level 5: Return on investment	Monetary benefits compared to the costs of training

and assess the impact of simulation-based education in hyperbaric medicine.

Methods

PROTOCOL

The protocol was developed *a priori* following 'A Measurement Tool to Assess Systematic Reviews' (AMSTAR-2) standards.[17] This systematic review is reported in adherence to the 'Preferred Reporting Items for Systematic Reviews and Meta-Analyses' (PRISMA) checklist.[18] The protocol (CRD42018111678) was registered with the International Prospective Register of Systematic Reviews (PROSPERO).

ELIGIBILITY CRITERIA

Eligibility criteria were predetermined. The population of interest was any healthcare provider (any profession or specialty providing care in hyperbaric medicine either as individual or as a team) at any level (trainees or not) or patients undergoing hyperbaric oxygen therapy. We included studies investigating simulation-based education. In this review, we used a broad conceptualisation of simulation including, for example, part-task trainers, full body mannequin, screen simulator, virtual reality, human simulation or a standardized patient. The goal of the simulation intervention could be either formative or summative assessment. When a comparator was present, it could be either no education, education with or without a simulation component, didactic teaching or any other comparative educational intervention. The outcome of interest was learning, which was categorized based on the Kirkpatrick model of educational outcomes, as modified by Phillips[19] (Table 1). Outcomes across all Kirkpatrick levels were included; however, from level 2b and above, studies relying only on self-reported outcomes were excluded because healthcare workers' self-assessments tend to be inaccurate and unreliable.[20,21] For levels 1 and 2a, we included self-assessed outcomes since this is the only option to explore these Kirkpatrick levels. All study designs were eligible for inclusion (e.g., observational, case series, experimental). Studies were only considered for inclusion if they were published in English in a peer-reviewed journal. Conference abstracts were not included.

SEARCH STRATEGY AND INFORMATION SOURCES

The search strategy was developed by an experienced information specialist (AD) in close collaboration with the research team (Appendix A). It was then reviewed by a second information specialist, following the 'Peer Review of Electronic Search Strategies' (PRESS) guidelines.[22] The databases MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials were searched without language restrictions, from inception to 19 September 2018. The reference lists of included studies were also searched in addition to the online 'Database of Randomized Controlled Trials in Diving and Hyperbaric Medicine'.[23] We also reviewed references of relevant book chapters[24,25] and consulted content experts for completeness and relevance of the final list of included studies.

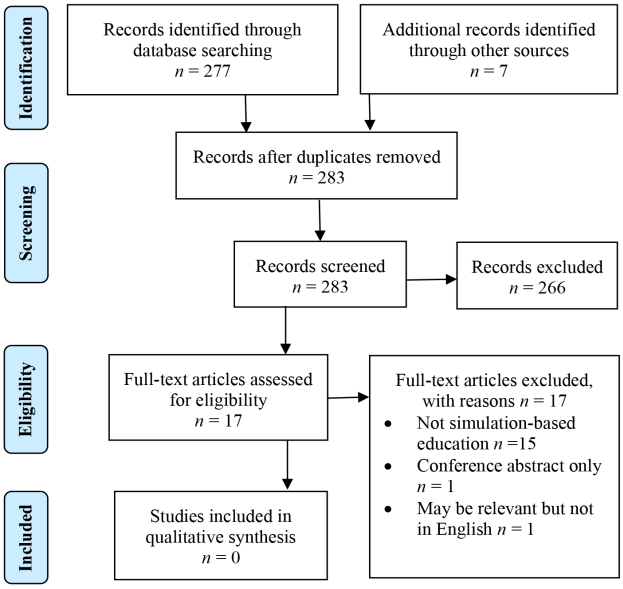
STUDY SELECTION

Identified studies were uploaded to a web-based systematic review software, DistillerSR (Evidence Partners, Ottawa, Canada), and duplicates were removed. A screening tool was developed by the research team and piloted with 20 randomly selected articles (Appendix B). This tool was iteratively refined until acceptable inter-rater reliability was established (minimum Kappa = 0.60). Pairs of independent reviewers (OCB, LM, TH) first assessed titles and abstracts for eligibility, followed by the full-texts of articles of included studies and those deemed 'unclear'. 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, NE).

DATA EXTRACTION

A data extraction form was developed and we planned to have pairs of independent reviewers to extract relevant information with DistillerSR. We planned to extract data including publication details (e.g., first author name, year of publication, country of data collection, funding, trial

Figure 1
PRISMA flow diagram for the literature search



registration), study characteristics (e.g., study design, sample size, inclusion/exclusion criteria), patient demographics, intervention and comparator details, the type of surgical procedure and anesthesia, and the effect of intervention on reported clinical outcomes.

RISK OF BIAS

The independent reviewers were expected to assess each included study for risk of bias using the 'Effective Practice and Organisation of Care Group' (EPOC) tool[26] for interrupted time series studies, repeated measures studies, non-randomized trials, cluster randomized trials, controlled before-after studies, and randomized controlled trials; and the 'Newcastle-Ottawa Quality Assessment Scale'[27] for cohort studies as appropriate.

DATA SYNTHESIS

We planned to conduct a narrative summary of results if included studies were heterogeneous and a meta-analysis if included studies were homogeneous.

Results

STUDY SELECTION

The search yielded 277 publications. An additional seven references were identified from book chapters and one duplicate was removed, leaving 283 references for title and abstract screening. Of these, 17 studies proceeded to full text-screening. After review of the full text of these articles, all 17 were excluded: one was published in German; one was a conference abstract; and 15 did not actually describe simulation-based education. Therefore, no article assessing the impact of simulation-based education in hyperbaric medicine and published in English was identified in this systematic review. The study flow is shown in Figure 1.

Although our inclusion criteria prespecified publication in English, we identified one article published in German that was relevant to simulation-based education and hyperbaric medicine.[28] According to the abstract published in English, this study reports the implementation and impact of in situ simulation training for emergencies in hyperbaric medicine. The authors concluded that mandatory yearly in situ simulation training of all hyperbaric medicine staff was well perceived and effective for improving performance (Kirkpatrick level 3).[28]

When consulting book chapters on education for hyperbaric medicine, we noted that the word "*simulation*" (or variations, e.g. simulated or simulator) was not mentioned at all by several references.[24,25,29–31] Others referred to simulation in statements such as "*some training in emergencies is necessary in a simulated form*"[32] but with no evidence to support this statement. The 'Educational and Training Standards for Physicians in Diving and Hyperbaric Medicine', produced by the Joint Educational Subcommittee of the European Committee for Hyperbaric Medicine (ECHM) and the European Diving Technical Committee (EDTC), recommended to "*treat a number of simulated diving casualties (probably at lesser depths) with the emphasis on the practical difficulties of a unit in a remote location*." However, the evidence to support this statement is unclear.[33]

Discussion

This systematic review is the first to assess the state of simulation-based education in hyperbaric medicine. No English language article assessing the impact of simulation-based education in hyperbaric medicine was identified. Only one potentially relevant paper published in German was found.

Our findings may be surprising given that simulation-based education has been widely adopted over the last two decades in most healthcare fields, including interprofessional education in acute care.[3,4,34] Hyperbaric medicine is interprofessional by nature as treatments require close collaboration between several professions, including physicians of different specialties, chamber operators, technicians, nurses and/or respiratory therapists.

While teamwork skills are important in routine hyperbaric oxygen treatments, they are even more crucial for life-threatening emergencies (i.e., crisis resource management (CRM) situations), which require coordinated and urgent actions between different professions for safe patient care. For example, when a hyperbaric patient develops a pneumothorax during treatment in a multiple place chamber, the physician, chamber operator and nurse must

communicate and coordinate effectively to quickly identify the complication and make the required treatment decisions. Examples of other crisis situations in hyperbaric medicine include seizure, cardiac arrest, and fire. Whether these crises occur in the operating room, intensive care, emergency department, obstetrics or hyperbaric medicine, positive patient outcome require optimal collaboration among interprofessional teams.

Interestingly, simulation-based education, including interprofessional simulation, has been largely adopted in many of these other fields. As defined by The World Health Organization, interprofessional education is "*when two or more professionals learn about, from, and with each other to enable effective collaboration and improve health outcomes*".[35] Interprofessional simulation typically aims to practice a simulated case together followed by a debriefing. Both the simulated practice and the debriefing are done as a team, which allows participants to learn with and from each other. For example, simulated practices for operating room interprofessional teams show long-term translation of positive communication and teamwork behaviours in clinical settings.[36] Simulated practice for multidisciplinary critical care unit teams led to subsequent improved teamwork and patient management.[37] Overall, evidence seems to consistently show that simulation-based education translates to improved behaviours of healthcare professionals into their clinical setting and is promising for improving patient outcome.[6] Evidence is particularly strong for the positive effect of interprofessional simulation on CRM skills of teams.[3] Hyperbaric medicine seems to be an exception to interprofessional simulation-based education, even though it requires effective teamwork in managing urgent conditions and responding to life-threatening complications.

This systematic review highlights the need for the hyperbaric medicine community to take concrete actions to join the evidence-based simulation education movement occurring in other healthcare disciplines. Currently, teaching in hyperbaric medicine is largely limited to didactic teaching, and simulation-based education is not part of any existing certification course. Simulation training is only occasionally conducted at hyperbaric conferences, such as the hyperbaric emergency team simulation course, hosted by the Canadian Undersea and Hyperbaric Medical Association.[38] One possible next step to advance simulation-based education in hyperbaric medicine may be to develop, implement, and evaluate a standardized simulation curriculum across hyperbaric centers.

Although this systematic review identifies an important knowledge gap in hyperbaric medicine, some limitations should be noted. Specifically, we included only published studies in English. However, only one potentially relevant non-English study was identified. We also focused only on hyperbaric rather than diving medicine; however, our inclusion criteria were relatively broad as we considered all Kirkpatrick levels and most study designs.

Conclusions

This systematic review found no English language publication assessing the impact of simulation-based education in hyperbaric medicine. More research is needed to determine how the hyperbaric medicine community and their patients may benefit from simulation-based education to optimize both practice and patient care.

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Appendix A

Literature search algorithm

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process and Other Non-Indexed Citations and Daily <1946 to 2018 September 19>

Search Strategy:

1 Hyperbaric Oxygenation / (11224)
2 hyperbaric oxygen*.tw,kw. (9380)
3 hyperbaric chamber*.tw,kw. (773)
4 hyperbaric medicine.tw,kw. (295)
5 or / 1-4 (13637)
6 SIMULATION TRAINING / or COMPUTER SIMULATION / or PATIENT SIMULATION / (180403)
7 simulat*.tw,kw. (453193)
8 Virtual reality / or virtual reality.tw,kw. (7711)
9 Manikins / (4590)
10 (manikin* or mannikin* or mannequin*).tw,kw. (4072)
11 high fidelity.tw,kw. (7020)
12 CURRICULUM / or curriculum.tw,kw. (85625)
13 "*Internship and Residency*" / (44153)
14 exp Education, Medical / (152716)
15 or / 6-14 (756026)
16 5 and 15 (203)

Database: Embase Classic+Embase <1947 to 2018 September 19>

Search Strategy:

1 hyperbaric oxygen therapy / (1492)
2 hyperbaric oxygen*.tw. (12264)
3 hyperbaric chamber*.tw. (1064)
4 hyperbaric medicine.tw. (378)
5 or/1-4 (13584)
6 manikin / (1194)
7 (manikin* or mannikin* or mannequin*).tw. (5967)
8 simulator / or simulation training / or patient simulation / or high fidelity simulation training / (13535)
9 simulat*.tw. (469033)
10 high fidelity.tw. (8362)
11 virtual reality / or virtual reality.tw. (16630)
12 exp medical education/ (307670)
13 curriculum / or curriculum.tw. (98179)
14 residency education/ (25781)
15 or/6-14 (836551)
16 5 and 15 (204)

Database: EBM Reviews – Cochrane Central Register of Controlled Trials <August 2018>

Search Strategy:

1 Hyperbaric Oxygenation / (335)
2 hyperbaric oxygen*.tw,kw. (889)
3 hyperbaric chamber*.tw,kw. (87)
4 hyperbaric medicine.tw,kw. (10)
5 or/1-4 (948)
6 SIMULATION TRAINING / or COMPUTER SIMULATION / or PATIENT SIMULATION / (2090)
7 simulat*.tw,kw. (12675)
8 Virtual reality / or virtual reality.tw,kw. (1782)
9 Manikins / (747)
10 (manikin* or mannikin* or mannequin*).tw,kw. (1327)
11 high fidelity.tw,kw. (579)
12 CURRICULUM/ or curriculum.tw,kw. (3607)
13 "*Internship and Residency*" / (1069)
14 exp Education, Medical / (2914)
15 or/6-14 (20049)
16 5 and 15 (17)

Appendix B

Screening questions

Screening 1:

1- Is this study about simulation-based education (could be training or assessment)?
Yes
No
Unsure

2- This study is about:
Hyperbaric medicine (most often includes hyperbaric oxygen treatment)
Diving medicine (does NOT include any hyperbaric oxygen treatment)
Unrelated field
Unsure

3- Is this reference an ORIGINAL study?
Yes, it is an original study (i.e. publication that aims to create new knowledge)
No, it is not an original study but rather repeats or combines existing knowledge
Unsure

4- This study looks like it is about simulation-based education AND hyperbaric medicine but is NOT in English
I confirm that it is NOT in English
It actually looks in English
Unsure

5- Open comment (e.g. note here duplicates when noticed)

Screening 2:

1- Is this study about simulation-based education (could be for training or assessment)?
Yes
No
Unsure

2- This study is about:
Hyperbaric medicine (most often includes hyperbaric oxygen treatment) Diving medicine (does NOT include any hyperbaric oxygen treatment)
Unrelated field
Unsure

3- Study design is:
Observational or case series → Include and go to question 4
Experimental (RCT, quasi randomized)
Quasi experimental (CBA, ITS)
Case report
Other (specify)
Unsure

*4- Is this study about training (simulation **for** learning) or assessment (simulation **of** learning, i.e., test)?*
Training
Assessment
Both
None
Unsure

5- This paper meets one of the exclusion criteria:
It is NOT published in English
It is NOT published in a peer-reviewed journal
It only measures outcomes with self-assessment
It is only a conference abstract
Other (justify)

6- Open comment (e.g., note here duplicates when noticed)

Is there a role for hyperbaric oxygen therapy in the treatment of refractory wounds of rare etiology?

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Key words
Calciphylaxis; Economics; Epidemiology; Hyperbaric medicine; Review article; Skin; Nitric oxide

Abstract
(Longobardi P, Hoxha K, Bennett MH. Is there a role for hyperbaric oxygen therapy in the treatment of refractory wounds of rare etiology? Diving and Hyperbaric Medicine. 2019 September 30;49(3):216–224. doi: 10.28920/dhm49.3.216-224. PMID: 31523797.)
Introduction: Delayed wound healing indicates wounds that have failed to respond to more than 4–6 weeks of comprehensive wound care. Wounds with delayed healing are a major source of morbidity and a major cost to hospital and community healthcare providers. Hyperbaric oxygen therapy (HBOT) is a treatment designed to increase the supply of oxygen to wounds and has been applied to a variety of wound types. This article reviews the place of HBOT in the treatment of non-healing vasculitic, calcific uremic arteriolopathy (CUA), livedoid vasculopathy (LV), pyoderma gangrenosum (PG) ulcers.
Methods: We searched electronic databases for research and review studies focused on HBOT for the treatment of delayed healing ulcers with rare etiologies. We excluded HBOT for ulcers reviewed elsewhere.
Results: We included a total of three case series and four case reports including 63 participants. Most were related to severe, non-healing ulcers in patients with vasculitis, CUA, LV, and PG. There was some evidence that HBOT may improve the healing rate of wounds by increasing nitric oxide (NO) levels and the number of endothelial progenitor cells in the wounds. HBOT may also improve pain in these ulcers.
Conclusion: We recommend the establishment of comprehensive and detailed wound care registries to rapidly collect prospective data on the use of HBOT for these problem wounds. There is a strong case for appropriately powered, multi-centre randomized trials to establish the true efficacy and cost-effectiveness of HBOT especially for vasculitis ulcers that have not improved following immunosuppressive therapy.

Introduction

The definition of a 'problem' or 'non-healing' ulcer or wound varies considerably depending on the context and geography. For the purposes of the current review, we have used the following definitions.

Problem wound: any wound where there are one or more local complicating factors, such as exudate, infection and/or systemic comorbidities, such as diabetes or polypharmacy.

Delayed wound healing: applies to any wound that fails to respond to 4–6 weeks of comprehensive wound care, does not heal or recurs.[1] This is often a consequence of being a problem wound where the complicating factors have been poorly appreciated. While wound healing does not need to be complete within 4–6 weeks, a wound healing trajectory should be established within that time frame.

Wounds are a major source of morbidity and a major cost to hospital and community healthcare providers. There appears to be a knowledge deficit on how to adequately manage problem wounds, given the low healing rates reported; for example, 50% of venous leg ulcers remaining unhealed after one year of treatment.[2]

Many problem wound types have been reviewed in the context of HBOT over the past ten years. The tenth European Consensus Conference on Hyperbaric Medicine in 2016 reviewed burns, compromised skin grafts and flaps, and diabetic foot ulcers (DFU).[3] The Cochrane Collaboration® have published reviews of acute surgical and traumatic wounds (2013) and chronic wounds due to diabetes, venous ulcers and arterial ulcers (2015).[4,5] These types of wounds have been excluded in the current review.

Review

EPIDEMIOLOGY

Chronic wounds constitute a significant health problem. They are common and reduce the quality of life of those affected. The true incidence, cost and health impact are difficult to assess accurately given the wide range of disease, the fact

Table 1
Prevalence, annual incidence and cost of wounds related to systemic connective tissue disorders (vasculitis) in Europe (28 member countries)

Adult population (2018) = 510,381,379[7]		
Vasculitic wounds		
Prevalence* (adult population)	11.5 per 100,000	59,006 patients
Cost per wound** (mean)	€8,850[52]	
Indicative annual cost (mean)	€522 million per year	
*The prevalence increases significantly with age (up to 60 per 100,000 women aged 75–79)		
** up to €13,800 per wound with a persistence time longer than two years		

that much care is delivered at home and that many wound care products are purchased directly in some countries. Evidence on the total number of patients receiving wound treatment in a local population is limited. The prevalence of open wounds could be estimated as being from 120–320 per 100,000 (0.12–0.32%) in the western population.[6] Applying these rates to the population of Europe (in 2018)[7] suggests that between 615,000 and 1.64 million individuals have an open wound at any one time.

Epidemiologic studies show that up to 80% of leg ulcers have a vascular etiology (venous, peripheral arterial disease, or mixed).[8] Epidemiologic studies conducted in dedicated wound healing clinics have found that 6.6–23.0% (average 14.8) of ulcers are associated with autoimmune disease including vasculitis (Table 1), rheumatoid arthritis, scleroderma, systemic lupus erythematous, psoriasis, and pyoderma gangrenosum.[9–11] A study from the Mayo Clinic found that ulcers occurred at a rate of 1.8 leg ulcers per 100 person-years in a population of 813 rheumatoid arthritis patients followed for 9,771 person-years.[12] In that study, 6% of ulceration episodes ultimately required amputation and in the rheumatoid arthritis population, leg ulcers were associated with increased mortality (Hazard Ratio (HR) 2.42; 95% CI 1.71 to 3.42). Leg ulcers in this population were associated with age (HR 1.73 per 10-year increase; 95 % CI 1.47 to 2.04), rheumatoid factor positivity (HR 1.63; 95% CI 1.05, 2.53), presence of rheumatoid nodules (HR 2.14; 95% CI 1.39 to 3.31) and venous thromboembolism (HR 2.16; 95% CI 1.07 to 4.36).

Most wound care costs arise in the hospital sector: 27–30% of acute hospital beds are likely to be occupied on any day by patients with a wound.[6] With regard to surgical wounds with surgical site infections (SSIs), the standardized infection ratio is influenced by many factors including the type of operation and age. In Europe, in 2013–2016, the overall cumulative incidence of SSI was highest in open colonic surgery (10.4%, range 5.8–18.4) and lowest in knee prosthesis (0.5%, range 0.1–1.4). The incidence density was also highest in open colonic surgery (6 SSI per 1,000 post-operative patient days) and lowest in knee prosthesis (0.1 in-hospital SSI per 1,000 post-operative patient-days). It is important to note an increase of the percentage of SSIs in laminectomy operations in 2012–2015 (0.9%, range 0.2–2.4).[13] SSIs are twice as common in patients over 64 (RR 1.6; 95% CI 1.2 to 2.3).[14] An acute hospital performing 10,000 surgical procedures annually may have 300–400 surgical wounds with SSI at a cost of 3,300–4,400 excess bed-days or 1.74–2.32 million Euros.[15,16] Surveillance of surgical wounds with SSI and prevention are considered very important. Burns exert a catastrophic influence in terms of human life, suffering, disability, and financial loss. Burns are estimated to cause approximately 180,000 deaths annually worldwide, mostly in low- to middle-income countries. Burns accounted for the primary diagnosis in 424,000 visits to emergency departments in the United States in 2014, while in 2016 there were approximately 40,000 burn-related hospitalizations in the United States, 30,000 of which were at specialized burn centers. Work-related burns account for 20–25% of all serious burns.[17]

This review describes the delayed healing ulcers associated with rare etiologies such as autoimmune disease including vasculitis, calcific uremic arteriolopathy (CUA), livedoid vasculopathy (LV) and pyoderma gangrenosum (PG).

WOUND PATHOPHYSIOLOGY

Chronic wounds are often associated with poor perfusion and one near-universal characteristic of chronic wounds is that the wound tissues are pathologically hypoxic.[1,18,19] Normal wound healing proceeds through an orderly sequence of steps involving control of contamination and infection, resolution of inflammation, regeneration of the connective tissue matrix, angiogenesis and epithelialization. Several of these steps are critically dependent upon adequate perfusion and oxygen availability.

The result of this process is a sustained restoration of anatomical continuity and functional integrity. Problem wounds are those that have failed to proceed through this orderly sequence of events and have therefore failed to establish an anatomic and functional result. This failure of wound healing is usually the result of one or more local wound or systemic host factors inhibiting the normal tissue response to injury, including persistent infection, poor perfusion and hypoxia, cellular failure and unrelieved pressure or recurrent trauma.[18]

Not all non-healing wounds are hypoxic but pathological hypoxia is correlated with impaired wound healing and increased rates of wound infection.[19] Fibroblast replication, collagen deposition, angiogenesis, resistance to infection

and intracellular leukocyte bacterial killing are oxygen sensitive responses essential to normal wound healing.[4] Steep oxygen gradients from the normally perfused wound edge to the hypoxic wound center may also play a role in stimulating normal wound healing.[20]

Pressure ulcers are localized injuries to the skin and/or underlying tissue, usually over a bony prominence, due to pressure or pressure in combination with shear forces. Common areas involved are over the sacrum, calcaneus and ischium. The superficial skin is less susceptible to pressure-induced damage than deeper tissues, and the external appearance may underestimate the extent of injury. Pressure ulcers are typically related to immobility but can also result from poorly fitting shoes, casts or other medical equipment.[21]

STANDARD MANAGEMENT OPTIONS

Many factors are associated with chronic ulceration and a multidisciplinary approach is required in the assessment of these patients. The goals are to ascertain the pathogenesis, make a definitive diagnosis and choose the optimal treatments to achieve healing within a given time. A correct diagnosis is essential to avoid inappropriate treatment that may cause deterioration of the wound, delay in wound healing, or harm to the patient.[1] The primary determinant of specific management strategies is the basic etiology of the wound in question.

The general principle in treating problem wounds is to simultaneously address the underlying pathology and institute both systemic and local treatments designed to improve the local wound environment. A wide range of therapies are available, including pressure-relieving mattresses, negative pressure wound therapy, growth factor therapies and tissue-engineered dermal substitutes.[22] In practice, wound management is often a sequential search for a successful combined approach. HBOT should be one element of such a combined approach.

RATIONALE FOR HBOT USE

HBOT involves breathing 100% oxygen in a compression chamber and is designed to increase the serum partial pressure of oxygen and oxygen diffusion into the target tissue. HBOT is increasingly used as an adjunctive treatment in many problem wounds. Regardless of the primary etiology, a common contributor to delayed healing is hypoperfusion. Evidence exists to demonstrate that intermittent oxygenation of these wounds, achievable only during HBOT exposure, can encourage normalization of wound healing processes and hasten the healing trajectory.[23,24]

HBOT produces an increase in plasma oxygen content directly proportional to the increase in alveolar oxygen tension in accordance with Henry's Law. This greatly increases the effective diffusion distance for oxygen down a steep pressure gradient, making more oxygen available for cellular metabolism. The availability of oxygen is an important rate-limiting factor for several aspects of wound healing.

Local hypoperfusion and hypoxia may also be the result of an interaction between vascular endothelium damaged by trauma, infection or hypoxia and circulating leucocytes. Neutrophils are activated by damaged endothelium and chemo-attraction results in microvascular plugging and hypoperfusion. In a series of elegant experiments, Thom has clearly demonstrated that HBOT (and not normobaric oxygen) inhibits the adherence and sequestration of neutrophils by inhibiting $\beta 2$ integrin function while also inducing antioxidant enzymes and anti-inflammatory proteins.[25,26]

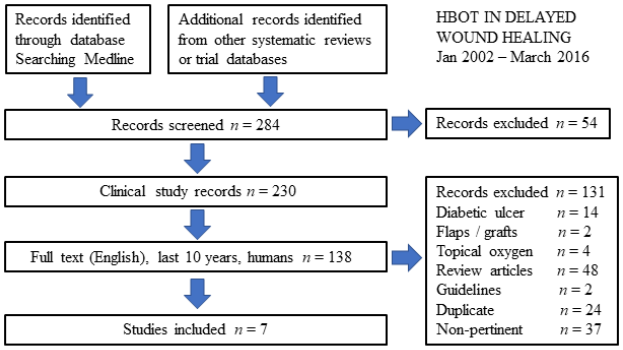
Neutrophils, fibroblasts and macrophages are all dependent upon oxygen to achieve specific inflammatory or repair functions. Both improved leukocyte-mediated bacterial killing and antibiotic potentiation have been demonstrated.[23,24] In addition, high oxygen tensions inhibit the production of a range of bacterial toxins, allowing increased host resistance to infection.[23] Hyperoxia increases synthesis of reactive species derived from inducible Nitric Oxide Synthase (iNOS) and myeloperoxidase, leading to excessive S-nitrosylation of cytoskeletal β actin.[25]

Importantly, HBOT does not reduce neutrophil viability and functions such as degranulation and phagocytosis remain intact.[26] A separate anti-inflammatory pathway for HBOT involves impaired pro-inflammatory cytokine production by monocyte-macrophages and has been shown in animal models and humans.[27] This may be the basis for reduced levels of circulating pro-inflammatory cytokines under stress conditions.[28] The molecular mechanism is unknown, but could be related to HBOT-mediated enhancement of haemeoxygenase-1 and heat shock proteins (e.g. HSP 70).[29]

Control of healing has been described as taking place via 'waves' of reactive oxygen species (ROS), lactate and nitric oxide (NO) production. In chronic, non-healing wounds HBOT has been shown to produce a persistent increase in NO in wound fluid associated with increased granulation tissue formation and wound closure.[30] ROS appear to be among the most important signals that control the healing process. Oxidative stress plays a positive role during angiogenesis and involves hypoxia-inducible factor (HIF) and vascular endothelial growth factor (VEGF) signaling. The full picture is emerging, but recent studies have identified several pathways that are VEGF-independent.[31]

As well as the above, HBOT has been associated with a suite of other effects that may play an important role in stimulating wound healing. HBOT and lipoic acid supplementation can downregulate an existing chronic inflammatory state, changing the protease/anti-protease levels within the wound microenvironment. A concomitant decrease in matrix metalloproteinase-9 expression, together

Figure 1
Flow diagram. Literature analysis, between January 2002 and March 2016, for Hyperbaric Oxygen Therapy in the treatment of refractory wounds of rare etiology. Seven publications have been included with different treatment of 63 individuals from three rare etiologies for chronic wounds: non-healing vasculitic ulcers that had not improved following immunosuppressive therapy, patients with calcific uremic arteriolopathy (CUA), livedoid vasculopathy (LV) and pyoderma gangrenosum (PG)



with increased levels of platelet derived growth factor contribute significantly to acceleration of the dermal wound repair process.[32]

HBOT also produces a transient increase in basic fibroblast growth factor production by fibroblasts and may inhibits transforming growth factor beta-1 production. Daily HBOT (202.6 kPa, 2 atmospheres absolute pressure (atm abs)) selectively stimulates fibroblast proliferation after seven days. Lower or higher levels of HBOT do not appear to have this effect.[33]

Finally, HBOT augments the release of stem/progenitor Cell (SPCs) from bone marrow through a NO dependent mechanism associated with the wound repair process.[34] The population of CD34 haematopoietic progenitor cells in peripheral circulation doubled in response to a single HBOT exposure at 202.6 kPa and increased eight-fold over the course of 20 treatments.[35] The net result of these mechanisms is improved local host immune response, clearance of infection, enhanced tissue growth, angiogenesis and a positive healing trajectory.

EVIDENCE REVIEW OF HBOT USE

Our review of HBOT in ulcers of rare etiology assessed the evidence from January 2002 to March 2016 and was originally undertaken for the tenth ECHM European Consensus Conference on Hyperbaric Medicine in Lille (France).[3] We undertook a Medline search using appropriate MeSH terms finding a total of 284, but after elimination of those investigating wound etiologies reviewed elsewhere, studies not relevant to HBOT, reviews or guidelines and duplicates, we were left with four case series and three case reports.[36–43] These include differing treatment of 63 individuals with non-healing vasculitic ulcers that had not improved following immunosuppressive therapy, in patients with CUA, LV, and PG[36–43] (see Figure 1).

In general, positive responses were reported with the use of HBOT. In the first case series 11 patients with end-stage renal disease and dialyzed for an average of 163 (SD 84) months had treatment for distal ulcers with an average of 40 sessions at 2.5 atm abs (for details see Table 2). Two patients could not be evaluated (one patient interrupted HBOT after 10 sessions, one patient died due to ventricular arrhythmia after eight sessions). Eight completely healed and survived to 1-year follow up, with no recurrence of skin lesions. One deteriorated leading to foot amputation.[36] In the second case series reporting 35 patients with severe, non-healing, vasculitic wounds not improved following immunosuppressive therapy, 20 sessions of HBOT at 2 atm abs were associated with complete healing in 28 (78%), partial healing in four (11.4%), no improvement in 3 (8.6%).[37] In the third case series, an average of 28 sessions of HBOT at 2 atm abs was associated with healing in 11 of 12 patients with wounds due to CUA in end-stage renal failure.[38,39]

In the first case report, in a 43-year-old patient presented with deteriorating CUA two years after kidney transplantation. The authors started iloprost (a synthetic analogue of prostacyclin PGI_2 used as a vasodilator) and HBOT at 2.5 atm abs for a total of 19 sessions. The wounds became clean and there was no further necrosis. Transcutaneous oxygen pressure ($PtcO_2$) around the wounds improved from 18 to 25 mmHg. Two large wounds were then covered with cultivated autologous skin cells (keratinocytes and fibroblasts) to further enhance epithelialization. Seven months later the wounds were healed and remained so the four-year follow-up period. The authors recommended robust trials in a larger sample of patients to verify these findings.[40]

In the second case report, two patients with LV were treated with HBOT at 2.5 atm abs for 10 and 17 daily sessions respectively with wound healing and pain relief for recurrent multiple non-healing ulcers involving the feet and ankles.[41]

In the third case report a refractory vasculitic toe wound, in a 14-year-old girl suffering from systemic lupus erythematosus (SLE), was treated with HBOT at 2.6 atm abs for 16 sessions with subsequent healing of that wound.[42]

Finally, in the fourth case report a 15 year-old girl with PG affecting the inguinal and suprapubic region and the right upper limb was treated with HBOT at 2.5 atm abs for 10 sessions with complete healing and relief of pain.[43]

While we have made every effort to locate further unpublished data, it is very likely this review is subject to a positive publication bias, with generally favorable cases more likely to be reported.

Table 2

Literature published January 2002 to March 2016, for HBOT in refractory wounds of rare etiology. This review does not include the wounds already considered in the tenth European Consensus Conference on Hyperbaric Medicine in 2016 (burns, compromised skin grafts and flaps, diabetic foot ulcers),[3] or analyzed by The Cochrane Collaboration® reviews on acute surgical and traumatic wounds (2013) and chronic wounds due to diabetes, venous ulcers and arterial ulcers (2015).[4–5]

Non-healing vasculitic ulcers that had not improved following immunosuppressive therapy						
Ref number	***n***	**Outcome measure**	**Patients**	**HBOT protocol**	**Results**	**Comment**
37	35	Healing	Aged ≥18 years with severe, vasculitis-induced ulcers	202.6 kPa (2 atm abs), 90 min, 20 sessions, 5 times per week	Complete healing 28 (80%), partial healing 4 (11.4%), no improvement 3 (8.6%)	Favours HBOT Moderate
42	1	Healing	14-year-old girl with refractory vasculitic ulcer (systemic lupus) of the toe over three months	263.4 kPa (2.6 atm abs), 90 min, 16 sessions.	Ulcer healed after 16 sessions	Favours HBOT
Patients with calcific uremic arteriolopathy (CUA), livedoid vasculopathy (LV) and pyoderma gangrenosum (PG)						
40	1	Healing	43-year-old male with CUA 2 years after kidney transplant. Despite intensive standard treatment his wounds progressed. Treated with iloprost + HBOT+ skin substitute	253.3 kPa (2.5 atm abs), 90 min, 19 sessions	Complete healing 7 months after finishing treatment. Remained healed during the 4-year follow-up	Favours HBOT combined with iloprost and autologous cultured skin substitutes
36	11	Healing	Patients with end-stage renal disease (dialysis for mean 163 months) and distal ulcers	253.3 kPa (2.5 atm abs), 90 min, average 40 sessions (range: 20–108).	Two did not finish treatment. Eight completely healed with no recurrence at 1 year. One deteriorated (foot amputation)	Favours HBOT Moderate
41	2	Healing, Pain, QoL	LV with recurrent multiple non-healing ulcers involving feet and ankles and severe pain	253.3 kPa (2.5 atm abs), 60 minutes, 10 and 17 daily sessions for the 2 patients, 6 days a week.	Healing of the ulcers, pain relief	Favours HBOT
38, 39	12	Healing	Patients with CUA and skin ulcers, in end-stage renal disease	202.6 kPa (2 atm abs), 130 minutes. Average 28 sessions (range: 7–41)	11/12 demonstrated healing of wounds over an average of 6 weeks. The average duration of survival following successful treatment was 25.5 months (range 1.5–82)	Favours HBOT
43	1	Healing, pain, QoL	15-year-old female with PG; multiple ulcers in inguinal and suprapubic region, and right upper limb	253.3 kPa (2.5 atm abs), 90 minutes, 10 daily sessions	Complete healing	Favours HBOT

PATIENT SELECTION AND TREATMENT PROTOCOLS FOR HBOT

Assessment

HBOT is unlikely to accelerate tissue repair in wounds with normal oxygen tensions and it is essential to demonstrate reversible tissue hypoxia in the absence of surgically improvable arterial or venous disease before considering the use of HBOT.[44,45]

Transcutaneous oximetry (TCOM) is a simple non-invasive diagnostic technique that provides an objective assessment of local tissue perfusion and oxygenation. It can be used for serial assessment of the soft tissue envelope surrounding the problem wound. The role of TCOM in predicting wound healing remains a work in progress and the poor quality of the available clinical studies limits the interpretations of the available evidence.[46,47] Almost all data is obtained from patients with DFUs and the applicability to other wounds has not yet been systematically assessed. Currently, TCOM is a tool that will help predict if hypoxia is a factor contributing to poor wound healing in diabetic ulcers. In principle, a low transcutaneous oxygen ($P_{tc}O_2 < 40$ mmHg) while breathing air must show an adequate response to either or both of normobaric oxygen and HBOT administration.[48] The thresholds for what constitutes an adequate response is a matter of some controversy. While low $P_{tc}O_2$ values breathing air confirm wound hypoxia, they do not predict outcome with HBOT. A $P_{tc}O_2 > 200$ mmHg breathing HBO (253.3 kPa or 2.5 atm abs) is the best single discriminator between success and failure of HBOT (74% reliable).[48] Clinical practice guidelines are provided to use the available data to assist in identifying which patients will not heal spontaneously.[46]

CURRENT PROTOCOLS

The evidence to support HBOT is clearly very sparse for the target wounds in this review. No robust dose-finding trials exist for HBOT, therefore many different protocols are used for delivery of oxygen in clinical practice. Hammarlund and Sundberg used a treatment session of 243.1 kPa (or 2.4 atm abs) for 90 minutes, five days a week to a total of 30 sessions over six weeks.[49] With some minor variations, this is a common schedule for chronic wound management, although in some countries a schedule employing 202.6 kPa (or 2 atm abs) pressure is more common.

HBOT is associated with some risk of adverse effects including barotrauma to ears, sinuses and lungs, temporary worsening of short-sightedness, claustrophobia and oxygen toxicity.[5] Although serious adverse events are rare, HBOT cannot be regarded as an entirely benign intervention.

COST IMPACT OF HBOT

The cost of wound care has been estimated at 2.5–3.9 million € per 100,000 individuals.[6] A typical course of treatment with standard wound care for six to eight weeks may cost €1,744 (USD 2,000) per week, with an estimated €10,463 to €13,951 (USD 12,000–16,000) for dressings alone; €1,308 (USD 1,500) in materials and supplies, €436 (USD 500) in fees to the hospital or wound care center. Among patients with partial foot amputation wounds up to the trans-metatarsal level with evidence of adequate perfusion, fulfilling 8 weeks of treatment, the average weekly total cost for patient treated by negative pressure wound therapy is €2,994 (USD 3,338) compared to €4,353 (USD 4,853) for standard moist wound therapy.[50]

Our best estimate is that approximately 11.5 wounds per 100 thousand inhabitants are related to rare etiology such as systemic connective tissue disorders (vasculitis) and CUA.[9–11] This suggests that in Europe's 28 member countries (2018), there is an average of 59,000 patients at any one time suffering from a vasculitis-related wound and the corresponding costs for these wounds are likely to be €522 million per year.[9,12,51] Of these wounds, 31.3% have a healing time of 12 months or longer, and over 24 months for 16.4%.[52] The average cost per wound (healing time average cost) for a patient with 2 or more comorbidities is €3,900. The longer the wound healing time, the higher the treatment cost, that is up to the average cost of €13,800 per wound with a healing time of 24 months or longer.[52] Assuming that HBOT maintains the wound healing trajectory within average times (15 weeks, 107 days; SD 150), based on the Fife 2012 data, we can claim that HBOT could lead to an average healing cost saving of €9,900 (€13,800–€3,900) per each refractory wound of rare etiology treated by HBOT as part of a multidisciplinary treatment plan.

The high cost of wound care has stimulated the development of combined care models designed to diagnose and treat such wounds efficiently in the primary care and outpatient setting, with care escalating to inpatient when required. HBOT administered in an outpatient hyperbaric and wound care center may significantly reduce the number and cost of inappropriate admissions.[51]

Caring for a patient with chronic ulceration is complex and necessitates multidisciplinary collaboration to achieve the goal of providing comprehensive wound care. The combined use of HBOT with other advanced wound healing modalities may be a useful synergy in the armamentarium of wound healing. Niezgoda reported improvements in treatment of compromised post-surgical and arterial wounds. The combination of negative pressure wound therapy and HBOT produced results better than when either was used alone.[53]

Unfortunately, there is little direct evidence on the cost-effectiveness of HBOT in the treatment of acute and chronic wounds.[54] Although there is some evidence suggesting effectiveness, none of the studies in this review measured utilities or expressed their health outcomes as QALYs.

The lack of available evidence on economic endpoints is striking, given the fact that HBOT is widely applied in the problem wounds settings and is reimbursed by insurance companies in Europe and the USA for the treatment of chronic wounds.[55] Further studies should include economic outcomes in large clinical studies of strong methodological quality to make recommendations on the cost-effectiveness of applying HBOT in wound care.

While the gold standard for evidence will remain large, well-constructed RCTs, there is an important supportive role for epidemiological studies and clinical registries to confirm and quantify benefit.[52] To this end, we believe the initiation of a European register of wounds would be a valuable advance in improving our knowledge about in general wound management and the use of HBOT in particular.

Conclusions

Based on the case series and case reports available, from January 2002 to March 2016, HBOT may be effective in ulcers exhibiting delayed healing and associated with rare etiologies such as vasculitis, CUA, LV and PG. Assessment for HBOT should be recommended for problem wounds, especially those that have failed to respond to more than four weeks of comprehensive wound care or when healing is not predicted within four to six weeks of standard of care.

In clinical practice, physicians should set clear clinical targets and rigorously measure patient-based outcomes to better understand the impact of adding HBOT to any established wound care regimen. In assessing patients for treatment, physicians should provide documentation of vascular screening and evidence that appropriate action has been taken to optimize vascular flow prior to the institution of HBOT. TCOM is a useful tool to predict whether hypoxia is contributory to delayed wound healing.

Trials of high methodological rigor are required to properly establish the place of HBOT in the therapeutic pathways of these wounds. These trials should include common agreed HBOT protocols and a robust cost-utility analysis. While waiting for the completion of appropriate RCTs, we recommend the establishment of comprehensive wound registries to improve clinical practice.

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The world as it is

A diver's guide to subaquatic envenomation in the Mediterranean

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Abstract
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Introduction: Between 40,000 and 50,000 divers and swimmers are envenomated each year and diving as a hobby is becoming increasingly popular. In the Mediterranean, envenomation is most often by Weever fish, Scorpion fish and jellyfish but coral and sea urchins may also be venomous.
Envenomation: Most stings cause local inflammation, oedema and pain. The severity of pain varies with the venom and the amount injected. In severe cases, stings may be life-threatening due to cardiogenic or anaphylactic shock or penetration of vital structures.
Management: Most cases of envenomation are preventable with a combination of measures including the avoidance of contact through good buoyancy control, the wearing of body-suits, and by maintaining visual awareness. Immediate management is to return to the surface, elevate and wash the site of injury. Immersion in hot water followed by simple analgesics for pain relief has been shown to be more effective than other methods. More severe cases should be identified by symptoms including confusion and heavy bleeding and referred to qualified medical care.
Conclusion: Envenomation by subaquatic species is common and preventable yet the dissemination of the appropriate knowledge is limited. This knowledge summary provides pertinent information aimed at divers in preventing and managing such injuries.

Introduction

It is estimated that greater than 1,200 species of fish may be venomous[1] and many other marine species are known to also produce venom. These mostly inhabit tropical waters and several of these species are found in the Mediterranean. Symptoms of envenomation are typically pain, swelling and erythema but are wide ranging, from an innocuous and temporary burning sensation to shock, haemorrhage and rarely death depending on the type of venom, dose, individual patient and site of envenomation. Diving is rapidly growing in popularity and there are now estimated to be up to six million recreational divers globally.[2] Each year, between 40,000 and 50,000 divers and swimmers are envenomated,[3] some of which are fatal. In the Mediterranean, envenomation is most often by Weever fish, Scorpion fish and jellyfish but coral and sea urchins may also be venomous.[4]

'Venomous species' are defined as those which possess toxin-secreting glands and a mechanism capable of delivering this, such as a spine or tooth. This is distinct from 'poisonous species', where the toxin is present in the skin or flesh of the species and there is a lack of a delivery mechanism, meaning that ingestion of the poisonous species is the only means of transferring the toxin.

Venomous species are not aggressive but defensive, and only sting when threatened. Diving as a passive observer of subaquatic life rather than attempting to touch it is an effective avoidance measure. Awareness of the risk and the adoption of simple measures can also help prevent envenomation.

A literature review and liaison with the British Royal Navy's Institute of Naval Medicine identified a lack of concise resources available to the diver on the prevention and management of envenomation injury and on the quick identification of high-risk venomous subaquatic species. This work is intended to provide an overview of prehospital management of envenomation by subaquatic species with special reference to species endemic to the Mediterranean Sea.

Envenomation

The delivery of venom is by the insertion of a hypodermic delivery mechanism.[5] In most cases, this takes the form of a sharp barb, spine, or tooth which serves as a defence to an aggressor species. Jellyfish are distinct as they have tentacles used to entrap and envenomate prey (all described further below). Once the hypodermic mechanism is inserted,

a toxin-producing gland at its base secretes toxins which are transferred through the mechanism and into the aggressor. From here the toxin enters the circulation and lymphatic system causing localised and sometimes systemic effects.

The means of delivery are various. Stingrays have a whip-like barbed tail that stabs a victim with force causing a deep wound. This causes traumatic injury as well as envenomation.[6] Stingrays are bottom dwellers and so envenomation in humans often follows accidental treading on the ray in shallow water. This means wounds are often to the legs but can be to the thorax and abdomen. Deaths have occurred when wounds to the chest have resulted in heart penetration.

Fish possess sharp spines which cause minor penetrative injury to the site and local pain. Once inserted, the spine sheath ruptures and the venom is released into the wound. Like stingrays, many venomous fish (e.g., Weever fish), are bottom feeders and may cause envenomation when stepped on. Minor lacerations from penetrative trauma are concomitant. A notable exception and newcomer to the Mediterranean is the Lionfish, which swims above the seabed and has a very noticeable fan-like appearance and dangerous sting.

Jellyfish have a complex venom containing various enzymes and proteins which cause pain and sometimes systemic effects. They do not cause puncture wounds but discharge venom into the skin through thousands of tiny hypodermic spines called 'nematocysts'. Patients often have multiple stings from long tentacles which can mean delivery of a large dose of venom.[4] Jellyfish are slow, translucent and inhabit much of the water column. This makes them pervasive and difficult to spot, meaning divers may be stung by swimming into the jellyfish by accident. Most stings are mild, however potent stingers include the Portuguese man o' war and Mediterranean box jellyfish, both of which cause extremely painful stings. It should be noted that the Mediterranean box jellyfish is distinct from other species of box jellyfish found elsewhere in the world which possess potentially fatal stings.

Finally, sea urchins reside on the seabed and have extremely sharp barbs which snap off on penetration and cause multiple wounds. They easily puncture body suits and injury is often local to the lower leg and foot due to being trodden on.[7]

Symptoms

LOCAL EFFECTS

Most stings cause local inflammation, swelling and pain. The severity of pain varies with the venom and the amount injected and may last from one hour to more than a day, and often resolves spontaneously. The severity of the sting is determinant on the envenomating species, the dose, site of envenomation and the individual physiology of the victim. The puncture site may contain a foreign body remnant from a stingray barb or sea urchin which may cause infection if left in situ. In the case of barbs, these are difficult to remove and attempts to do so may cause further damage unless removed by a medical professional.

SYSTEMIC EFFECTS

Some species are particularly venomous, including the Portuguese man o' war jellyfish. Stings to the trunk and multiple stings may cause a systemic effect which may be life-threatening. Systemic symptoms include nausea, vomiting, headache, dizziness and low blood pressure. Allergic reactions may present on envenomation and in extreme cases this may develop to anaphylaxis (extreme allergic response) and shock.[8] However, it should be noted that this is rare, and even rarer in the Mediterranean.

Prevention

Many cases of envenomation occur in divers who were not wearing the appropriate protective clothing or inadvertently came in to contact with a venomous species. This may be through intentional touching on the part of the diver or by poor buoyancy control leading to contact with the sea bed and thus bottom dwelling species.

PROTECTION

Covering of bare skin and wearing of footwear is effective in preventing contact with many venomous spines and filaments. Full-body suits should always be worn, even in warmer waters. These can either be neoprene wetsuit, dry suit or lycra skin suit in warm water and include hood and gloves.[9] Exposure of the face is hard to avoid and it is therefore vulnerable to stinging, especially in the space between mask and regulator. This makes environmental awareness especially important.

BUOYANCY

Many species of venomous fish inhabit the sea bed in sand or rock and are often difficult to spot. For this reason, touching the seabed is unwise and avoided through good buoyancy control. Good buoyancy also minimises kicking of fins which also agitates the seabed and may also instigate defensive behaviour by any species making the area their home.

AWARENESS

Many stings, especially from jellyfish, occur due to inadvertently swimming into the venomous species. Divers should take special care to look in the direction they are headed, including during ascent, in order to maintain visual awareness.[10]

TOUCHING

Do not touch. This is a general rule for divers to avoid

Figure 1
Schematic of pre-hospital care of a patient with envenomation injury

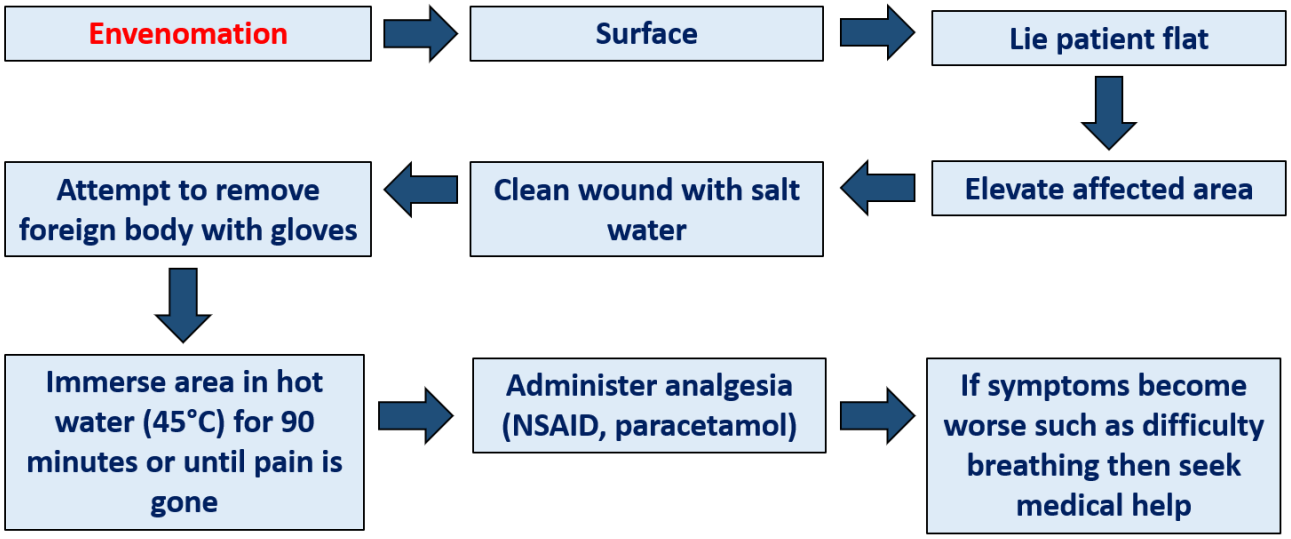
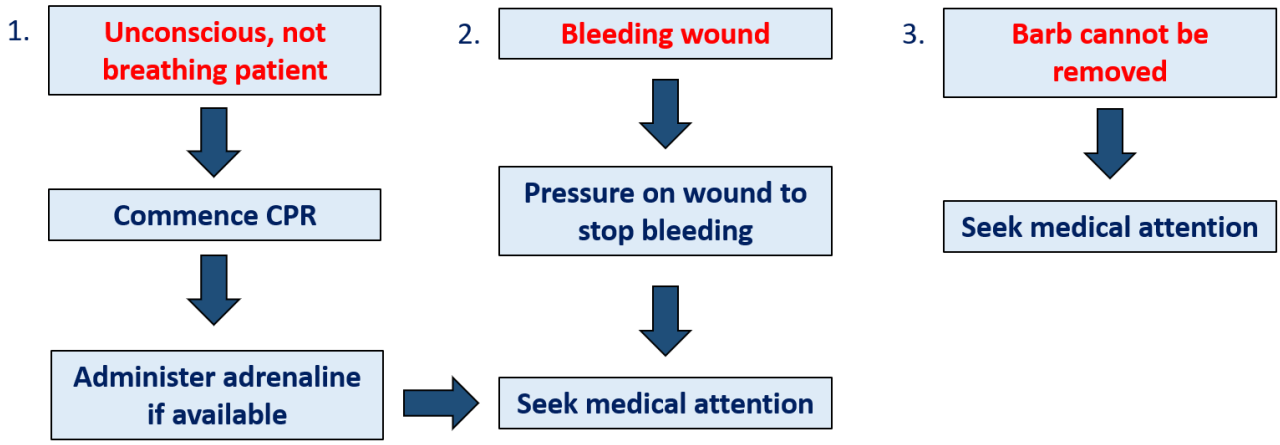


Figure 2
Schematic of pre-hospital care of a patient with serious envenomation injury



damage to subaquatic life but is especially important in the avoidance of stings. Most fish are naturally shy and avoid an approaching diver by swimming to a safer distance. However, if a fish does not retreat from you or adopts a defensive posture, it may be that it has an alternative defensive mechanism such as venom. In this situation it is best for the diver to move away.

Immediate management

If stung during a dive, immediate action should be taken to return to the surface (Figure 1).[5] This is for several reasons. Firstly, to reduce the risk of further envenomation. Secondly, the physiological effects of the toxin are unlikely to be known and it is therefore safest to return to the surface where the air supply is not dependent on the user being conscious and on delivery by breathing apparatus. Finally, medical treatment will be located ashore or aboard.

On surfacing, the affected area should be elevated to reduce blood flow to the area and thereby reduce inflammation and swelling.[5] The area should be rinsed with sea water to remove any toxin which may still be at the surface and any foreign body carefully removed if possible. A caveat to this is stingray wounds where any barb remnant should be removed only by a medical professional due to the risk of bleeding. Jelly fish stings should not be rubbed to avoid stimulating injection of further toxin. The affected area plus some contiguous unaffected skin (or another unaffected part of the body) should be immersed in hot water of not more than 45ºC for up to 2 hours or until the pain subsides. Hot water immersion has proved more effective at pain reduction than both vinegar and cold water in multiple studies.[4] Most toxins are heat labile and will be denatured in heat. The insertion of unaffected skin is to avoid inadvertent scolding if the effect of the toxin is to numb the affected area to sensation.

Pain relief may be given. This should initially be paracetamol or non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin and ibuprofen.[11] The wound should be cleaned with salt water to prevent infection. Further medical attention should considered if the pain cannot be controlled.

In rarer cases further management is needed (Figure 2). Where the wound is deep, such as with stingray, copious bleeding may occur. This should be stopped by applying pressure to the wound and dressing with bandages, and medical attention sought. Even where there is minimal bleeding, stingray wounds should always be reviewed by a medical practitioner as there is a risk of subsequent infection.

If the patient displays confusion, drowsiness or any other worsening of symptoms medical attention should be sought immediately. These are systemic symptoms and may be a sign of anaphylaxis or shock. Under these circumstances cardiopulmonary resuscitation may be required if the patient becomes unconscious and stops breathing. Adrenaline should be administered if available for cardiac arrest or anaphylaxis.

Conclusion

Envenomation by subaquatic species is common and preventable yet the dissemination of the appropriate knowledge is limited. This is compounded by the non-availability of a concise and usable resource for divers to be used before and while diving. This knowledge summary provides pertinent information aimed at the layman and is a document of intent for a portable publication on prevention, identification and prehospital management of subaquatic envenomation in the Mediterranean.

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Case report

A case report of cerebral arterial gas embolism (CAGE) associated with Takotsubo cardiomyopathy

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Key words
Barotrauma; Hyperbaric oxygen therapy; Pulmonary barotrauma; Pulmonary oedema; Recreational diving; Salt water aspiration; Scuba

Abstract

(McCool D, Butler C, Evans J, Aase C. A case report of cerebral arterial gas embolism (CAGE) associated with Takotsubo cardiomyopathy. Diving and Hyperbaric Medicine. 2019 September 30;49(3):229–232. doi: 10.28920/dhm49.3.229-232. PMID: 31523799.)

A 43-year-old female scuba diver was retrieved and treated following a rapid ascent and presumed cerebral arterial gas embolism (CAGE). She subsequently developed respiratory distress and was found to have Takotsubo cardiomyopathy, with transient left ventricular dysfunction, elevated cardiac enzymes, and normal CT coronary angiography. We believe this to be the first report of CAGE associated with Takotsubo cardiomyopathy.

Introduction

Pulmonary barotrauma (PBT) with cerebral arterial gas embolism (CAGE) is a known risk of scuba diving. Respiratory compromise following CAGE is common, and is often a result of non-fatal drowning in the disabled diver.[1] Gas embolisation of the coronary circulation is also described, and can cause cardiac dysfunction.[2]

Takotsubo cardiomyopathy (TCM) is a pattern of cardiac dysfunction seen in situations following high sympathetic stimulation such as subarachnoid haemorrhage and ischaemic stroke.[3,4] It may also occur in otherwise uneventful diving, presenting as immersion pulmonary oedema.[5] TCM is described in a case of iatrogenic gas embolization,[6] but has not previously been described in divers suffering from CAGE.

We present a case of a diver suffering from CAGE who developed severe pulmonary oedema requiring intubation and mechanical ventilation, secondary to TCM.

Case report

A previously well 43-year-old female diver on the first dive of the day developed mask problems at the beginning of the dive, and ascended rapidly from a depth of 17 metres' sea water (msw). She was symptom free at depth but lost consciousness on surfacing. Her dive instructor observed her to be blue and limp, inflated her buoyancy compensator and retrieved her to the boat. She remained unresponsive for up to 10 minutes.

After regaining consciousness she vomited, but displayed no gross neurological abnormalities. She was coughing with mild shortness of breath, but no chest pain. Helicopter retrieval to the nearest hospital was arranged, with her initial management consisting of high flow oxygen. In view of the likely diagnosis of CAGE she was kept supine. She was noted at the time of retrieval to have bilateral respiratory crepitations, peripheral oxygen saturation (SpO_2) of 95% on 8 L·min^{-1} of oxygen via a non-rebreather face mask, and an elevated respiratory rate (number of breaths per minute not recorded).

On arrival at hospital, approximately two hours after surfacing from the dive, she had a Glasgow Coma Score (GCS) of 15, and no focal neurology or evidence of pulmonary barotrauma. She had a tachycardia of 120 beats per minute, a respiratory rate of 35–40 breaths per minute, and required supplemental oxygen to maintain the SpO_2 above 95%. Blood tests demonstrated haemoconcentration, a metabolic acidosis, and a PaO_2:FiO_2 (P:F) ratio of 155 (normal around 500). A chest X-ray showed bilateral alveolar infiltrates that were considered to be in keeping with salt water aspiration, but no radiological evidence of pulmonary

barotrauma (e.g., pneumothorax). An ECG demonstrated a sinus tachycardia with no acute ST segment elevation or Q waves to suggest a myocardial infarction. A provisional diagnosis of resolving CAGE with salt water aspiration was made, and transfer to our centre for hyperbaric oxygen therapy was arranged. One litre of intravenous crystalloid was administered, and high flow oxygen continued.

On arrival for recompression she remained neurologically intact with a sinus tachycardia of 128 bpm, blood pressure 127/87 mmHg, an SpO_2 of 98% on 15 $L \cdot min^{-1}$ of oxygen. Her ECG was unchanged. Widespread crepitations were noted on chest auscultation. In view of the risk of further embolization by residual gas trapped in the pulmonary veins or heart chambers, or neurological deterioration, she was recompressed with an RN62 recompression table (US Navy Treatment Table 6). She received oxygen via a hood system.

During the hyperbaric treatment she developed increasing respiratory distress and diaphoresis, with desaturation during the air breaks. There was no chest pain. Towards the end of the treatment, the patient was expectorating pink frothy sputum. On completion of recompression she required intubation and ventilation for progressive hypoxaemia. Pulmonary oedema fluid was noted in the endotracheal tube. Repeat chest X-ray again demonstrated bilateral fluffy opacification, and there continued to be no radiological evidence of pneumothorax. Flexible bronchoscopy showed the endotracheal tube to be in good position, a small amount of clear watery secretions in the trachea, but no evidence of aspiration or segmental collapse.

After arrival in the intensive care unit (ICU), transthoracic echocardiography (TTE) showed global left ventricular dysfunction with an ejection fraction (EF) of 20–25% with mid-ventricular akinesia. The heart was otherwise structurally normal, with no evidence of outflow obstruction. The appearance was consistent with a mid-ventricular stress cardiomyopathy. The ECG now showed an inverted T wave in lead I, and a flattened T wave in V6. The T waves were biphasic in leads II, III, and aVF. There was no ST segment elevation. Sinus tachycardia and hypotension were treated with a small fluid bolus and vasopressors. Low dose milrinone was added empirically to improve ventricular function. The patient remained sedated, intubated and ventilated for 36 hours. During this time she remained neurologically stable. Her sedation was ceased and she responded to verbal commands with no evidence of focal neurological deficit and a P:F ratio over 300. She was extubated with an SpO_2 of 98% (inspired oxygen fraction 30%). Bedside TTE prior to extubation revealed a substantial improvement of the LV dysfunction with visual estimate of EF of 45–50% (at around 34 hrs after ICU admission, and 48 hrs after the dive).

The patient's Troponin I peaked at 2956 $ng \cdot L^{-1}$ (normal < 10). Computed tomography coronary angiography demonstrated a coronary calcium score of 0. The coronary circulation was normal other than an aberrant origin of the right coronary artery (RCA); a slit-like origin from the ascending aorta above the sino-tubular junction on the left side, superior to the origin of the left coronary artery. The initial course of the RCA ran between the aorta and the main pulmonary artery. The left anterior descending (LAD) artery was described as a type III vessel with no disease and no myocardial bridging. Exercise stress testing was performed 10 days after the dive, with the patient exercising to 9.7 metabolic equivalents (MET) with no ECG changes or chest pain. The test was stopped due to dyspnoea and dizziness. The right ventricle was normal in size and function on multiple TTEs over the course of the patient's hospital admission. Magnetic resonance imaging (MRI) of the brain showed evidence of a small infarction in the right post-central sulcus consistent with the diagnosis of CAGE, but no other abnormalities. The patient denied experiencing chest pain at any time before or during her admission.

At follow-up three weeks following the dive she was completely well with resolution of all symptoms. Repeat TTE at this time showed normal left ventricular systolic function with an EF of 67%.

Discussion

Given this diver's history of a rapid ascent, loss of consciousness on surfacing and brain MRI evidence of infarction, it is likely that the primary pathology in this case was pulmonary barotrauma leading to CAGE.

The typical natural history of CAGE is for a sudden onset of neurological abnormality followed by a partial or complete recovery. Relapse can follow due to re-embolisation by gas still in the pulmonary veins or cardiac chambers, or due to inflammatory changes in the injured brain and cerebral vessels. Initial recovery is primarily due to the redistribution of bubbles through the cerebral circulation, in part due to a hypertensive response to the brain injury.[7–9]

Takotsubo cardiomyopathy (TCM) was first described in 1991, and is often characterized as 'stress cardiomyopathy'.[10] The commonest (but not only) form is apical ballooning of the left ventricle from which the term 'takotsubo' takes its name. The Mayo Clinic criteria specify, as one of the criteria, "*transient hypokinesis, akinesis, or dyskinesis in the left ventricular mid segments with or without apical involvement; regional wall motion abnormalities that extend beyond that expected from a single epicardial vascular distribution*".[10] Isolated mid-ventricular and basal LV dysfunction / isolated mid-ventricular LV dysfunction (apical-sparing TC) is a described variant.[11] Stress cardiomyopathy may be found in approximately 2% of patients presenting with probable myocardial infarction, however it has a relatively low mortality of 1–2%, and recurrence is less than 1%. The average clinical recovery time is approximately 18 days. The condition occurs most commonly in older individuals with a high female

predominance. The aetiology is unknown. It often follows a severe emotional shock although many triggering events have been reported. Stress cardiomyopathy is diagnosed first by suspicion, often in the context of apparent coronary artery disease. Echocardiographic findings are regional hypokinesia or akinesia, predominantly in the left ventricle (although the right ventricle can be affected). The extent of the regional ventricular muscle dysfunction is usually outside expected coronary artery territory, and the diagnosis should be confirmed by angiography showing no significant coronary disease. It may be accompanied by ECG changes of ST elevation and/or a significant troponin rise. During the recovery phase, the use of beta blockers and afterload reduction is considered beneficial.

The precipitation of TCM following non-diving intracerebral events such as subarachnoid haemorrhage and ischaemic stroke is described.[3,4] Subarachnoid haemorrhage in particular is associated with an extreme sympathetic response with high levels of circulating catecholamines, which is one of the proposed mechanisms of the myocardial injury in TCM.[10,11]

We were able to find a single case in the literature of a case of TCM which was precipitated by iatrogenic CAGE whilst undergoing a computed tomography-guided transthoracic needle biopsy.[6] This case demonstrated a typical pattern of TCM with apical ballooning, raised cardiac enzymes and normal coronary angiography. The ventricular dysfunction resolved five days following the event.

Villela et al. reported a case of a previously well 34-year-old diver who had a likely CAGE, with troponin rise, akinesis of the apex of the left ventricle and hypokinesis of the mid infero-septal segment, an EF of 50% and normal coronary angiography.[12] Two weeks later, the regional wall motion abnormalities and ventricular function had normalised. Their case differs from ours in that their patient reported significant chest pain responding to vasodilator therapy, and the development of pericarditis. The authors suggested the pathology was likely to be coronary artery gas embolism, with TCM a possible alternative.

The differential diagnosis of respiratory failure in our case includes immersion pulmonary oedema, coronary gas embolism, or aspiration with non-fatal drowning. Non-fatal drowning does not explain the severe cardiac dysfunction, unless as a separate cause of TCM.[13] Coronary gas embolism does not explain the pattern of myocardial dysfunction seen on echocardiography. Nor is it explained by occlusion of the RCA at or near its origin. Immersion pulmonary oedema is also unlikely as the respiratory symptoms were not present at depth, the water was warm (27–29 degrees Celsius), and the dive did not involve severe exertion.[14] The respiratory symptoms were absent at depth, worsened following exiting the water and further during recompression, which is more in keeping with pulmonary oedema due to left ventricular failure. The nature of the deterioration during the course of the recompression may relate to the increased afterload for the left heart due to systemic vasoconstriction. Alternatively, it may have represented pulmonary oxygen toxicity superimposed on already impaired respiratory function.

There are a number of reports and case series of cardiomyopathy developing in seemingly uneventful dives, and this may represent a subset of divers who develop immersion pulmonary oedema, although the exact mechanism is unclear.[14–17]

Conclusion

We believe this case is the first to describe Takotsubo cardiomyopathy in a diver suffering from CAGE. We think the diagnosis should be considered in divers suffering from CAGE who develop respiratory distress or cardiovascular instability.

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Errata

In a review article (Hoencamp E, van Dongen TTCF, van Ooij PJAM, Wingelaar TT, Vervelde ML, Koch DAA, van Hulst RA, Hoencamp R. Systematic review on the effects of medication under hyperbaric conditions: consequences for the diver. Diving and Hyperbaric Medicine. 2019 June 30;49(2):127–136. doi: 10.28920/dhm49.2.127-136. PMID: 31177519.) Table 1 was labelled twice, meaning that the subsequent tables were labelled incorrectly. The correct table labelling now appears in our electronic version online for download by Society members, and will be correct in PubMed Central®'s full text version. The error will persist if accessed through Elsevier, Clarivate, the National Library of Australia and in the small number of print copies distributed.

Obituary

John Knight, MB, BChir (Cantab), Dip Obs, FFARACS, FANZCA, Dip DHM, RFD 1930–2019

John studied medicine at Cambridge University (Gonville and Caius College) and at St Bartholomew's Hospital, London, qualifying in 1953. In 1954, he took a short service commission in the Royal Navy during which he visited Melbourne during the 1956 Olympic Games, whilst serving on *HMS Newcastle* as it toured the Far East. This was when he decided that Australia would become his home, and in 1959, he, his wife Gillian and infant son arrived on the *SS Iberia*, settling first in South Australia and then in Morwell, Victoria.

As a general practitioner, he became concerned about the quality of anaesthesia being provided in the Gippsland region. The family moved in 1965 to Melbourne, where John held anaesthesia positions at several of the major hospitals in the region and joined the Grey Street Anaesthetic Group in 1966, receiving his FFARACS in 1969. In 1982 he was appointed Director of Anaesthesia at the Eye and Ear Hospital until his retirement from clinical practice in 1994. In the 1990s, he also ran the Diving Medical Service, providing medicals to occupational divers.

John was a member of the Royal Australian Naval Reserve (RANR) for over a quarter of a century. This was the genesis of his interest in diving; rostered to sit on the pier while the Reserve divers were in the water, he decided there must be a more interesting way to be involved and after a first ever dive at *HMAS Penguin*, he obtained a FAUI scuba certification in 1976. He was promoted through the ranks of the RANR, becoming Captain in 1980 and was awarded the Reserve Forces Decoration.

He was a prolific correspondent and contributor, publishing regularly in the *Australian Medical Journal*, *British Medical Journal* and *Lancet* as well as the *SPUMS Journal*. For some time after arriving in Australia, he wrote a regular column in the *Lancet* called "*A view from Australia*" comparing the British and Australian health systems. Following two tours to Vietnam during that war, he wrote a number of articles for the *Lancet*, *Anesthesiology*, *British Journal of Anaesthesia*, *British Journal of Surgery*, *Resuscitation*, etc. based on his experiences.

John Knight *was* SPUMS! Having joined the Society in 1972, he went on to serve on the Executive Committee for 27 years in the roles of Secretary 1975–1979, President 1979–1983, general committee member, Public Officer (the predecessor of the Education Officer) 1990–1995, Assistant Editor of the *SPUMS Journal* (Doug Walker as Editor) 1985–89, and then Editor of the Journal from 1990 to 2002. His practice address in Melbourne was used as the official SPUMS address from the time that he started as Secretary until SPUMS was incorporated in 1990.

Our Journal would not exist today if not for John Knight. In the early days, the contents of the journal were typed and layout created by manually cutting and pasting text onto A4 paper spread out on the dining room table to create camera-ready copy for the printer. By the time he handed over the editorship to Mike Davis in 2002, publication was computer-based. John developed a valuable relationship with our long-standing printer, Snap Printing in Hawthorn, a short walk from his home. An article well worth members reading on the history and development of the *SPUMS Journal* can be found on the Rubicon Foundation website.[1] In addition, he created a searchable database of all *SPUMS Journal* issues, each as a pdf file accompanied by a tab-separated index from the first issue in 1971 (a newsletter) to 2002. Originally this was made available as a CD that members could purchase. How best to provide this resource into the future for SPUMS members is still under discussion. His efforts to promote the Journal resulted in its first indexing on the Elsevier EMBASE medical database in early 2001. As his successor as Editor, John was an inspiration and continued to be a great support to me for several years.

Amongst his additional contributions to diving safety, he was instrumental in the design, promotion and distribution of the original 'safety sausage' and in the creation of a set of recreational air dive tables based on limits developed by Dr Bruce Bassett (our President and I still have copies of these tables which were released in 1985!).

In retirement John moved to live by the sea in St Leonards and indulged his significant skills in carpentry and woodworking before moving into aged care where he passed away on 09 May 2019, aged 89. John was an intelligent, warm and highly ethical man who will be greatly missed by those close to him. He has left an enduring legacy to diving medical education in Australia, New Zealand and beyond.

Reference

1 Knight J. The history and development of the South Pacific Underwater Medicine Society Journal. SPUMS Journal. 2001;31:215–20. [cited 2019 June 11]. Available from: http://archive.rubicon-foundation.org/xmlui/handle/123456789/7746.

Key words
Obituary; Writing – medical; Medical society; General interest

Michael Davis, Editor DHM 2002–2018

Notices and news

EUBS notices and news and all other society information is now to be found mainly on the society's website: www.eubs.org

EUBS President's message

Ole Hyldegaard

EUBS ExCom election

While writing this report preparations are in their final phase regarding the EUBS Scientific Meeting in Tel-Aviv 2019. Elections for a new EUBS ExCom Member-at-Large are now under way and the voting concluded at the time of publication of this issue of DHM. A fine list of distinguished candidates participated in the ballot. On behalf of the ExCom, I wish to congratulate all of the contenders for the vote of the new EUBS Member-at-Large; Gerardo Bosco from Italy, Miroslav Rozloznik from the Czech Republic and Akin Savas Toklu from Turkey. I hope many more members will feel encouraged to participate in our society work in the future.

***Diving and Hyperbaric Medicine*, upgrading of staff and future development**

As I have previously advocated, *Diving and Hyperbaric Medicine* (DHM) is going through a continuing process of formalized professionalism at both the operational and management level. This will require further financial support and important decisions will need to be addressed at the EUBS General Assembly which at the time of publication of my report will have already taken place. Our friends at the SPUMS organization- who largely administer DHM on behalf of both our organizations – operate under legal conditions described by local law as well as more administrative requirements for PubMed (NIH/NLM) accessibility of our e-journal. One cannot underestimate the importance for our field to have a scientific journal representing the medical specialities of diving and hyperbaric medicine in general. I am in support of strengthening our journal – also if this requires additional financial EUBS support, although such support will need to be adjusted within our organization's operational, economical capabilities – therefore, *this issue needs to be formally supported by the EUBS General Assembly and by the time you read this, this matter (and others) will have been presented and discussed at the GA in Tel Aviv.*

Key words
Medical society; General interest

Ole Hyldegaard
President, EUBS

EUBS Member at Large elections

As the EUBS Annual Scientific Meeting is being held in September, EUBS membership will now have elected a new Member-at-Large, and Dr Bengüsu Mirasoglu will have left office as Member-at-Large 2016. Associate Professor Gerardo Bosco will take his place in the ExCom as the new Member-at-Large 2019. ExCom extends their thanks to Dr Mirasoglu for her work in ExCom and we trust she will remain active within the Society. We also thank Dr Miroslav Rozloznik, PhD and Dr Akin Savas Toklu, MD for their engagement as candidates in this election – we hope to count on them in the future.

The new online voting process was much appreciated, and over 55% of our members voted. However, further feedback is appreciated, send an email to: secretary@eubs.org.

EUBS 2020 – First Announcement

Although our Annual Scientific Meeting in Tel Aviv, Israel, is just behind us, it is already time to think about next years' EUBS Annual Scientific Meeting, in Prague, Czech Republic, from 16–19 September 2020.

The meeting will be organised by a Local Organising Committee and chaired by Michal Hajek, MD, PhD, 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 will be 55 years since this field of medicine in this country has been established.

Prague is the capital and largest city in the Czech Republic, the fourteenth largest city in the EU and the historical capital of Bohemia. The city is home to about 1.3 million people, while its metropolitan area is estimated to have a population of 2.6 million. Prague has been a political, cultural and economic centre of central Europe complete with a rich history. It was founded during the Romanesque and flourishing by the Gothic, Renaissance and Baroque

eras. Prague was the capital of the kingdom of Bohemia and the main residence of several Holy Roman Emperors, most notably of Charles IV (1346–1378). It is located in the centre of the European continent, with direct air links with most European capitals and direct air connection from Frankfurt a. Main, Germany, for connecting to overseas flights to other continents.

Save the date! Prague, 16–19 September 2020

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 Members need your help

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. A new 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.

The Science of Diving

Support EUBS by buying the PHYPODE book 'The science of diving'. Written for anyone with an interest in the latest research in diving physiology and pathology. The royalties from this book are being donated to the EUBS.
Available from: Morebooks https://www.morebooks.de/store/gb/book/the-science-of-diving/isbn/978-3-659-66233-1

Hyperbaric oxygen lectures

Welcome to: http://www.hyperbaricoxygen.se/
This site offers publications and high-quality lectures from leading investigators in hyperbaric medicine. Please register to obtain a password via email. Once registered, watch online, or download to your smart device or computer for later viewing.
For information contact: folke.lind@gmail.se

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

Hyperbaric Oxygen, Karolinska

Welcome to: http://www.hyperbaricoxygen.se/

This site, supported by the Karolinska University Hospital, Stockholm, Sweden, offers publications and high -quality lectures from leading investigators in hyperbaric medicine. Please register to obtain a password via email. Once registered, watch on line, or download to your iPhone, iPad or computer for later viewing.

For further information contact:
Email: folke.lind@karolinska.se

The EUBS website is at
www.eubs.org

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.

Notices and news

SPUMS society information and news is to be found mainly on the society website: www.spums.org.au

SPUMS President's message

David Smart

Post graduate training in diving and hyperbaric medicine in Australia and New Zealand

Since SPUMS was founded on 03 May 1971, the organisation has always been a leader in diving medicine education. Historical records indicate that the Diploma of Diving and Hyperbaric Medicine (DipDHM) issued by SPUMS has been in existence since 1974, with the first Diplomates by examination receiving their awards in 1975.[1] This year is the 45th year of the SPUMS DipDHM, a continuous track record that precedes the modern specialist colleges ((Australian College of Emergency Medicine 1983, Australian and New Zealand College of Anaesthetists (ANZCA) 1992 – fully recognising ANZCA's longer-term evolution from a faculty of the Royal Australasian College of Surgeons). The whole process of administration of the SPUMS DipDHM has been voluntary, with the custodian being the SPUMS Education Officer. The structure of the DipDHM has been unchanged since the 1980's, requiring six months of diving/hyperbaric medicine clinical experience, successful completion of a two-week course in diving and/or hyperbaric medicine and successful completion of a peer-reviewed research project. The SPUMS DipDHM has the unique distinction of being referenced in the Australian Medicare Schedule for hyperbaric oxygen treatment, and indeed the DipDHM coincided with the first iteration of Medicare, "*Medibank*", which commenced in 1975.[2]

Until 2003, the SPUMS DipDHM was the only qualification in the field, and has been valued as an 'add-on' to other speciality qualifications, particularly for hospital practice in diving and hyperbaric medicine. In the last two decades, post-graduate training in diving and hyperbaric medicine in Australia and New Zealand has had additional providers. The University of Auckland administered a postgraduate Diploma in Medical Science – Diving and Hyperbaric Medicine, from 2004 to 2007. Some SPUMS members and other students undertook the this course or used its subjects as points towards the Master of Medical Science Degree. The course was wound up following a review in 2007.

In 2003, ANZCA developed its certificate program in diving and hyperbaric medicine, which extended for 10 years, being formally disbanded in 2013. The program extended the period of clinical experience in diving and hyperbaric medicine to 18 months (with a structured syllabus) and added a further two-week course in diving and hyperbaric medicine to the course requirements and an exit exam. Spanning 10 years, the ANZCA certificate stood as the higher qualification in the field, particularly for diving/hyperbaric Medicine specialists in hospital practice. Due to problems with operational supporting systems and structure, the certificate program was dissolved by ANZCA in 2013. This necessitated the building of a new post-graduate programme in diving and hyperbaric medicine from the ground up.

With enthusiastic input from diving and hyperbaric medicine specialists (all of whom were SPUMS members), and huge operational support from ANZCA at all levels, the ANZCA Diploma of Advanced Diving and Hyperbaric Medicine (ANZCA DipAdvDHM) was launched on 31 July 2017, under the governance of the ANZCA DHM Sub-Committee, based on the recommendations of the DHM Project Group. This diploma is now the highest-level qualification available in the field in Australasia. ANZCA has been very inclusive in its approach to the new qualification. The SPUMS DipDHM neatly dovetails into the first six months of the ANZCA DipAdvDHM. The latter qualification requires a total of 12 months of supervised clinical experience at an ANZCA accredited hyperbaric facility, as well as a second two-week course in diving and hyperbaric medicine, and satisfactory completion of an exit examination. The ANZCA program is accessible by medical practitioners from all specialty training programmes, provided they satisfy the pre-requisites documented by ANZCA.[3]

The first ANZCA examinations in diving and hyperbaric medicine were completed in July 2018 with one candidate successful. The second exams were completed 31 July 2019 with four candidates (three from Australia and one from New Zealand) being successful. The most recent examination cohort included senior specialists who registered to undertake the fellowship year, specifically for the DHM experience. Allowing for recognition of prior learning and previous ANZCA Certificate holders who were transitioned to the ANZCA DipAdvDHM, there are currently 19 ANZCA advanced diploma holders in Australian and New Zealand (not including this year's successful candidates).

From within this small group, there is great optimism and support to continue this program as the qualification that is required for clinical diving and hyperbaric medicine in Australia and New Zealand. The ANZCA DipAdvDHM course requires 12 months extra training in the field following speciality fellowship qualification. Australia and New Zealand now have a structured career path in diving and hyperbaric medicine that is equal to anything on offer in other countries. The structure is broadly summarised

Table 1
Summary of current post-graduate training in diving and hyperbaric medicine in Australia and New Zealand.

	Entry	6 months	12 months
Qualification: Basic medical degree +	Advanced trainee FANZCA FACEM FRACGP Other fellowship	SPUMS DipDHM (Fellowship not a requirement for SPUMS DipDHM)	ANZCA DipAdvDHM Must be in Fellowship year or post fellowship. Cannot receive award unless fellowship completed
Course work	Two-week course diving medicine or hyperbaric medicine	Either two-week course Diving and or Hyperbaric Medicine accepted by SPUMS/ANZCA, preferably early in term	Attend reciprocal two-week course eg Diving or Hyperbaric Medicine
Additional requirements	Prospective registration with ANZCA and SPUMS Current ALS	Complete research project. (marked by peer review)	Completion of ANZCA Training and documentation requirements (accepts SPUMS DipDHM research) Pass ANZCA written and viva exams
Practical experience		Six months total at accredited hyperbaric facility	12 Months total at accredited hyperbaric facility

in Table 1. SPUMS is particularly grateful to ANZCA for their inclusivity in assuming custodianship of this exciting initiative. I would encourage all doctors who are interested in diving and hyperbaric medicine to consider this qualification option. In addition, it is up to clinical leaders in all hyperbaric facilities around Australia and New Zealand to embrace this program and set up strategic processes for medical staff to achieve the qualification.

References

1 Knight J. Twenty-five years of SPUMS 1971-1996. SPUMS Journal 1996;26:95–105.

2 Australian Government Department of Health Medicare Benefits Schedule Book Category 3, operating from 01 May 2019. ISBN 978-1-76007-376-3. Available from: http://www.mbsonline.gov.au/internet/mbsonline/publishing.nsf/Content/1486E51EA54D9393CA2583D200168909/$File/201905-Cat3%203%20May%202019.pdf. p. 35. [cited 2019 August 07].

3 Australian and New Zealand College of Anaesthetists. Handbook for Advanced Diving and Hyperbaric Medicine Training, June 2019,Version 1.04. Available from: http://www.anzca.edu.au/documents/dhm-anzca-handbook-for-adv-dhm-training-20170405-v.pdf. [cited 2019 August 07].

Conflict of interest

Clinical Professor Smart is a member of the ANZCA Diving and Hyperbaric Medicine Sub-committee, and chair of the ANZCA Examination Committee in Diving and Hyperbaric Medicine.

Key words
Medical society; General interest

Clinical Professor David Smart
Hon President SPUMS

SPUMS 49th Annual Scientific Meeting

Diving Medical Support: Off the Beaten Track

19–24 April 2020

Venue: Oceans Resort, Tutukaka, New Zealand

The scientific programme for 2020 is coming together and looking good – '*Diving medical support: off the beaten track*', featuring our very own Richard Harris as Keynote Speaker. Add to that some of the best subtropical diving on the planet at the Poor Knights Islands Marine Reserve and this is an event not to be missed!

Conference website for more information and registration is here: http://www.spums2020.nz

See you in Tutukaka in April 2020.

Guest Speaker: Richard Harris, Adelaide
Convenor: Greg van der Hulst
Scientific Convenors: Hanna van Waart and Xavier Vrijdag

David Smart, AM

Clinical Professor David Richard Smart, BMedSci, MBBS(Hons), MD(UTas), FACEM, FIFEM, FAICD, FACTM, FUHM, DipDHM, ANZCA DipAdvDHM, AM, Medical Co-director and Senior Visiting Specialist, Department of Diving and Hyperbaric Medicine, Royal Hobart Hospital, Hobart, Tasmania and President of SPUMS was appointed a Member in the General Division of the Order of Australia (AM) in the June 2019 Queen's Birthday Honours. This recognition was for "*his significant service to hyperbaric medicine and to professional organisations*".

The Executive Committee and all members of SPUMS congratulate him on this award, which has certainly been richly deserved.

Michael Davis, Editor DHM 2002–2018

The SPUMS website is at
www.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.

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 http://www.anzca.edu.au/training/diving-and-hyperbaric-medicine.

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 2019

Viva examination: 25–26 October 2019, Brisbane

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 enquries should be submitted to dhm@anzca.edu.au.

The Australian and New Zealand Hyperbaric Medicine Group

Introductory Course in Diving and Hyperbaric Medicine 2020

Dates: 24 February–06 March 2020
Venue: Hougoumont Hotel, Fremantle, Western Australia
Cost: AUD2,600 for two 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*
Email: *fsh.hyperbaric@health.wa.gov.au*

Accommodation information can be provided on request

SPUMS Facebook page

Remember to 'like' us at:
http://www.facebook.com/pages/SPUMS-South-Pacific-Underwater-Medicine-Society/221855494509119

Royal Australian Navy Medical Officers' Underwater Medicine Course 2019

Dates: 14–25 October
Venue: HMAS Penguin, Sydney

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

Cost: AUD1,355 without accommodation
(tbc with accommodation and meals at HMAS Penguin)

For information and application forms contact:

Raj Karekar, for Officer in Charge
Submarine and Underwater Medicine Unit, HMAS Penguin, Middle Head Rd, Mosman, NSW 2088, Australia
Phone: *+61-(0)2-9647-5572*
Email: *Rajeev.Karekar@defence.gov.au*

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 www.spums.org.au or at 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 January 2016, the SPUMS Academic Board consists of:

Dr David Wilkinson, Education Officer, Adelaide;
Professor Simon Mitchell, Auckand;
Dr Denise Blake, Townsville.

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

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

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.

Scott Haldane Foundation

As an institute dedicated to education in diving medicine, the Scott Haldane Foundation has organized more than 290 courses all over the world, over the past 25 years.

SHF is increasingly targeting an international audience with courses world wide. Below are the upcoming SHF-courses in 2019 and early 2020.

The courses Medical Examiner of Diver (part I and II) and SHF in-depth 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).

2019
05 October: Refresher course 'Organization diving medical', Utrecht, NL
09–16 November: Medical Examiner of Divers part 1, Nosy be, Madagascar
16–23 November: 27th SHF In-depth course diving medicine (2d), Nosy be, Madagascar
23–30 November: 27th SHF In-depth course diving medicine (2d), Nosy be, Madagascar

2020
27–28 March: Medical Examiner of Divers part 1, Zeist, NL
02–04 April: Medical Examiner of Divers part 2, Amsterdam Ac Med Centre, NL
May: Medical Examiner of Divers part 2, Bonaire

On request
Internship HBOT (level 2d certification), NL/Belgium
Internship different types of diving (level 2d), NL/ Den Helder/Royal Dutch Navy

The course calendar will be supplemented regularly.

For the latest information: http://www.scotthaldane.org

Capita Selecta Diving Medicine

The Capita Selecta Diving Medicine of the University of Amsterdam annually offers symposia presented by speakers of international renown to a multinational audience of diving physicians, paramedics and highly educated instructors. The level of the presentations is 'advanced' (1 and 2d of the European standard) and often beyond that. The lectures are in English.

Saturday 30 November 2019
Physiology and medicine of the metabolic and inert gases in diving

Topics include: O_2, CO_2, CO, He, N_2, Nitrox, He-mixtures, saturation, diagnosis, intoxications, HPNS, treatment
Speakers include: Jean-Claude Le Péchon (FR) and Mattijn Buwalda (NL)

www.capitaselectaduikgeneeskunde.nl.
Info: n.a.schellart@amsterdamumc.nl

Advertising in *Diving and Hyperbaric Medicine*

Companies and organisations within the diving, hyperbaric medicine and wound-care communities wishing to advertise their goods and services in *Diving and Hyperbaric Medicine* are welcome. The advertising policy of the parent societies appears on the journal website: http://www.dhmjournal.com

Details of advertising rates and formatting requirements are available on request from:
Email: editorialassist@dhmjournal.com

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DIVING HISTORICAL SOCIETY AUSTRALIA, SE ASIA

P O Box 347, Dingley Village
Victoria, 3172, Australia
Email: hdsaustraliapacific@hotmail.com.au
Website: www.classicdiver.org

Diving and Hyperbaric Medicine: Instructions for Authors (summary)

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, members of the diving and hyperbaric industries, and divers. Manuscripts must be offered exclusively to *Diving and Hyperbaric Medicine*, unless clearly authenticated copyright exemption accompanies the manuscript. All manuscripts will be subject to peer review. Accepted contributions will also be subject to editing.

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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 word count); structure of the article and abstract is at the author(s)' discretion.

Case reports, Short communications, Work in progress reports, etc: 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 and historical articles, Commentaries, Consensus and other meeting reports, etc., 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.

Formatting of manuscripts

All submissions must comply with the requirements set out in the full instructions on the DHM website. Non-compliant manuscripts will be suspended whilst the authors correct their submission. Guidance on the general structure for the different types of articles is given above.

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

- Instructions for authors (full version)
- DHM Key words 2018
- DHM Mandatory Submission Form 2018
- Trial design analysis and presentation
- EASE participation and conflict of interest statement
- English as a second language
- Guideline to authorship in DHM 2015
- Helsinki Declaration revised 2013
- Is ethics approval needed?

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Scholarships for Diving Medical Training for Doctors

The Australasian Diving Safety Foundation (ADSF) are proud to offer four 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 program. These scholarships are mainly available to doctors who reside in Australia. However, some 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 AUD3,000.

Interested persons should complete the Application Form at:
https://adsf.org.au/grants/scholarships/diving-medical-training and send it by email to johnl@adsf.org.au.
