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EDITORIAL COMMENTARY

Immersion pulmonary edema: drowning from the inside

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Immersion pulmonary (IPE, also known as swimming-induced pulmonary edema, SIPE) is a condition in which pulmonary edema develops rapidly during a dive or vigorous swim. Symptoms include dyspnea and hemoptysis. Physical exam reveals typical signs of bilateral pulmonary edema, which can be confirmed radiographically or with bedside ultrasound [1-3].

IPE tends to recur in susceptible individuals. Often there are cardiac or pulmonary comorbidities, but IPE can occur in highly fit individuals such as triathletes and military trainees: IPE has been reported among special forces units from both the United States and Israel. Why pulmonary edema, a condition typically associated with heart failure, should occur in normal individuals remains somewhat of a mystery.

Evidence supports the notion that IPE is a form of hemodynamic pulmonary edema. Immersion in water results in redistribution of blood from the legs and splanchnic vessels into the thorax, causing engorgement and increased pressure in pulmonary vessels, which is augmented by exercise. IPE was initially reported by Dr. Peter Wilmshurst, who observed that many victims subsequently developed hypertension [4]. Testing in his laboratory revealed an exaggerated increase in forearm vascular resistance in response to stimuli such as cold or oxygen breathing. He hypothesized that IPE is caused by the combination of exaggeratedly high afterload due to cold and increased preload due to immersion, which induces transient heart failure. Indeed, hypertension continues to be the most commonly described predisposing factor [1,3,5,6]. Besides hypertension, authors have described important comorbidities that include myocardial ischemia, cardiomyopathy including stress cardiomyopathy (SCM, including Takotsubo cardiomyopathy), cardiac valve disease, arrhythmias, small lungs, lung disease and excess fluid consumption. The cause of IPE in highly fit triathletes and military special forces trainees who have been screened medically has not been completely elucidated. However, hemodynamic studies during submerged exercise in cold water indicate that, compared to non-susceptible individuals, IPE susceptibility is associated with higher pulmonary artery and wedge pressures [7], thus predisposing to classic hemodynamic pulmonary edema. One possible risk factor in such cases may be reduced ventricular diastolic compliance, resulting in higher left ventricular filling pressures. Clinical evaluation of some IPE-susceptible individuals by the author has revealed an exaggerated hypertensive response to cold-water immersion. In such cases the resulting increase in circulatory afterload during cold-water exposure could provide a mechanism for transient heart failure as proposed by Wilmshurst [4].

Treatment of IPE is supportive: Once an IPE victim is removed from the water and warmed up, the hemodynamic conditions that predispose to IPE quickly reverse. Thus traditional treatments for hemodynamic pulmonary edema such as diuretics and vasodilators are not usually necessary. Supplemental oxygen is often required; inhaled β2-adrenergic agonists may also be helpful to accelerate expulsion of water from pulmonary air spaces [8].

In Wilmshurst's initial publication he provided evidence that cold water was an essential component of the pathophysiology. Indeed, a significant proportion of the now hundreds of reported cases occurred in cold water. To this list there are two new case series. Dr. Edmonds and colleagues have added 29 individuals from Oceania (warmer water) who experienced 41 IPE cases, of which 31 are described in detail [9]. His case series is accompanied by a thoughtful analysis [10]. These cases occurred from 2002-2018; median age was 55 years (range 21-72 years); females made up 55% of the cases; there were six deaths. Unlike other reported series in which surface swimmers constituted a large fraction [1], most of Edmonds' cases were in scuba divers. Cold water was implicated in only a small number of cases. Different from previous reports [1], the majority of Edmonds' cases were female.

Dr. Henckes and colleagues have reported a relatively large controlled study of divers experiencing IPE and controls. They collected data from a questionnaire received from 88 IPE victims and 392 controls. Mean age of the IPE victims was 50.9 years (vs. 45.3 years in controls); 47% were female (vs. 29.3% of controls).

What have we learned from these new case series? Edmonds' paper confirms observations of others that IPE can be fatal [11-14]. His case series also includes a large number of individuals with other underlying cardiac pathology, which emphasizes the benefit of investigation of IPE cases at the time of the event, especially with echocardiography. One particularly interesting observation in Edmonds' series is the high prevalence of SCM (26%), confirming the observations of Gempp [15], who in a series of IPE cases described reversible wall motion abnormalities, presumably a form of SCM. Edmonds and colleagues point out that the percentage of SCM cases in their recent series is probably an underestimate due to lack of detailed medical investigation of IPE cases in earlier years, while recently echocardiography has become fairly routine. An open question is whether SCM pre-existed the swim or dive, or did it occur as a result? It seems unlikely that someone with left ventricular impairment sufficient to induce heart failure (and therefore probably symptomatic) would entertain the notion of jumping in the water, especially for a scuba dive. The logical conclusion is that SCM is more likely to be triggered by the swim or dive rather than the reverse [16]. Evidence for this explanation is that exogenous epinephrine administration can induce Takotsubo cardiomyopathy [17-19]; thus the explanation for SCM in swimmers or divers is likely to be the effects on the heart of a rise in endogenous catecholamine levels during cold-water immersion [20-22].

In Dr. Henckes' series multivariable analysis was used to identify factors that may represent higher risk of IPE in divers. Her series nicely confirms risk factors previously published, including older age, female gender, hypertension and physical exertion [1,5,23,24]. While NSAID use has previously been suggested as a possible risk factor in a single case report [25], Henckes and colleagues have observed a statistically significant association (odds ratio 24.32). Whether this represents a specific risk of the medication or of the condition for which it was taken is a question requiring further investigation. Although not statistically significant, it is interesting that of the IPE group 4.5% reported a history of cardiomyopathy versus 2.3% of the controls.

A careful search for predisposing conditions is good practice in all IPE victims who have not already been medically screened. Hypertension remains the most common medical predisposing factor, most likely not only due to the increase in afterload, but also because accompanying left ventricular hypertrophy (LVH) may adversely affect diastolic function, causing elevated left ventricular end-diastolic pressure. For patients in whom hypertension is not evident during a clinic visit, ambulatory blood pressure monitoring may be helpful to detect masked hypertension [26], especially if LVH is observed on echocardiography.

Follow-up investigations that should also be considered in selected patients include examining for coronary artery disease and lung pathology. Recurrence is frequent in IPE, and good practice includes counseling IPE victims not to return to diving or competitive swimming until relevant medical conditions are treated.

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RESEARCH ARTICLE

Immersion pulmonary edema: case reports from Oceania

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ABSTRACT

Introduction: We aimed to document identified cases of immersion pulmonary edema (IPE) in divers from Oceania (the Indo-Pacific region) from January 2002 to May 2018, inclusive.

Method: Cases were identified using various sources, including searches of the Divers Alert Network Asia-Pacific (DAN AP) Fatality Database, published case reports, and interviews with survivors who had reported their incident to DAN AP.

Where available, investigations, pathology and autopsy results were obtained. Only incidents diagnosed as IPE by diving physicians or pathologists with experience in the investigation of diving accidents were included. Individual case histories and outcomes, together with brief individual summaries of the associations and possible contributing factors were recorded.

Results: Thirty-one IPE incidents in divers from Oceania were documented. There were two surface snorkelers, 22 scuba air divers and seven nitrox divers which included three closed-circuit rebreathers (CCR). The mean (SD) age was 53 (12) years, 58% of victims were females, and the average dive profile was to a maximum depth of 19 meters of seawater for 25 minutes. Six victims (19%) had previous episodes of IPE. There were nine recorded fatalities. Cardiac anomalies dominated the associated or possible contributing factors. These included valvular disease in 29%, transient cardiomyopathies in 26% and dysrhythmias in 16%.

Conclusions: Previously reported associations of IPE such as exertion, stress, cold exposure, negative inspiratory pressure, hypertension, overhydration, ascent or surfacing, tight wetsuit, aspiration and certain medications were identified. Cardiac conditions were frequent and included chronic disorders (valvular pathology, coronary artery disease) and transient disorders (dysrhythmias, transient myocardial dysfunction, takotsubo or stress cardiomyopathy). It is likely that the chronic cardiac disorders may have contributed to the IPE, whereas the transient cases could be either sequelae, contributors or coincidental to the IPE.

INTRODUCTION

Reviews have documented the history, clinical features, diagnosis, investigations, pathology, treatments, comorbidities and possible contributing factors for immersion pulmonary edema (IPE) [1].

We investigated 31 incidents of IPE in divers from Oceania (the Indo-Pacific region). Most occurred within Oceania and include all the regional cases of which we are aware from January 2002 to May 2018. The following is a summary of the individual cases, with references, indicating clinical and pathological aspects.

We have documented the individual IPE cases, their demographics, dive parameters, clinical history and investigations, while noting the associations or possible contributors in each case. The purpose of the paper is to provide a more detailed picture of the variety of scenarios associated with suspected IPE, and record how these have been managed

METHODS

For fatal cases, ethics approval was received from the Victorian Department of Justice Human Research Ethics Committee (to access data from the Australian National Coronial Information System); the Royal Prince Alfred Hospital Human Research Ethics Committee; the Coronial Ethics Committee of the Coroner's Court of

KEYWORDS: diving incidents; immersion; pulmonary edema; case reports; cardiovascular; deaths

Western Australia; and the Queensland Office of the State Coroner. In non-fatal cases victims provided informed, written consent to review and publish their medical and diving data in a non-identifiable form and provided these data for this purpose.

Cases included those reported to DAN AP by survivors, instructors and diving physicians from January 2002 to May 2018, inclusive. These were followed up with interviews where possible, as well as a review of clinical information and investigations.

In some cases, such as those involving fatalities, clinical information was not available. In others, only the formal conclusions were obtained regarding pathology tests and investigations. This is evident in the case reports. In most of these, medical histories, reports and discharge summaries were accessed, all with patients' approval. Any positive symptomatology, such as hypertension, was recorded. However, in the absence of specific documentation, negative clinical features were usually not recorded. Investigation results, both positive and negative, were recorded in the case histories.

A search was made of the DAN AP internal fatality database and associated autopsies for diving-related deaths in Australia during the same period. At autopsy, IPE needs to be differentiated from other disorders, especially drowning [1-5]. Thus, such cases associated with drowning and aspiration syndromes, pulmonary decompression sickness, pulmonary barotrauma, oxygen toxicity, other gas contaminations, and some marine animal toxicities, are excluded. In addition, a Medline search was conducted using the terms "diving," "immersion" and "pulmonary edema" to identify published cases within Oceania. Several of these cases were followed up with the authors in order to obtain further details.

Only cases validated by a diving physician or pathologist with experience in diving accident investigation were included. The main criteria were: symptomatology being related to immersion, clinical and radiological evidence of pulmonary edema, and/or consistent autopsy findings.

Demographic records were compiled and included: Age, gender, maximum depth of immersion, dive duration, type of diving (snorkel, scuba air, nitrox, rebreather), depth and time of incident commencement, diving experience and previous IPE incidents. The possible contributing factors, as suggested previously by others, were also noted when this information was available.

These cases often occurred in remote localities, and medical records were often incomplete. As a result, the prevalence of these possible contributing factors may be underestimated.

In most, the authors have commented on specific factors that may have been associated with the individual case but which have previously been observed in other series [1]. Some of these associations may have contributed to the IPE, but others may be coincidental or even consequences of the IPE.

RESULTS

CASE 1 (2002) [6,7]

The victim was a 51-year-old, healthy and physically fit female (body mass index/BMI of 24 kg/m^2) with no known cardiac history. During her 20 scuba dives over two years she experienced two episodes where she became exhausted, dyspneic, confused, cyanotic, panicky and required assistance. On another occasion she aborted the dive before submerging, as she had become dyspneic after a surface swim.

On her fatal dive, to a maximum of 12 meters of seawater (msw) for a total of 12 minutes, she performed three well-controlled ascents due to unspecified reasons. On the final surfacing, she was breathing heavily and panicking, although she remained conscious and coherent and swam to a mooring. Once there, her breathing deteriorated, she expectorated pink, frothy sputum and lost consciousness before being towed to shore. Cardiopulmonary resuscitation (CPR) was unsuccessful. Witnesses believed that she had not aspirated any water. Air consumption calculations indicated a respiratory minute volume (RMV) of 37 L.min^{-1}.

Autopsy

The autopsy showed pulmonary edema, resuscitation artefacts and cerebral edema. There were no supportive signs of drowning. Hilar node sarcoidosis was identified, but there was no evidence of pulmonary barotrauma (PBT) or coronary artery disease (CAD). Structural cardiac pathology was detected at autopsy. This included mitral and tricuspid valve degeneration with ballooning of the tricuspid valve and microcalcification of the bundle of His. The myocardium exhibited contraction band necrosis.

Comments

Although unclear of its import in this case, mitral valve degeneration may be associated with mitral incompetence and propensity to increased pulmonary vascular pressures and pulmonary edema. It may be associated with dysrhythmias as well.

Contraction bands are often associated with takotsubo cardiomyopathy (TC) and other stress cardiomyopathies

(SCM) [8-10] but are a non-specific post mortem indicator of stressed myocardium from various causes. The sympathomimetic influences which could contribute to TC/SCM/transient myocardial dysfunction (TMD) include the observed anxiety/panic episodes – and exertion in this case. There is no supportive evidence that these disorders were contributory. Without appropriate premorbid investigations, these differential diagnoses would be conjectural only.

Three previous transitory incidents were consistent with IPE.

CASE 2 (2002) [11]

A 31-year-old female with no relevant medical history and using no medication was undertaking her second pool dive at a depth less than 4 meters for 90 minutes in a water temperature of 20°C. She developed dyspnea, a wheezy cough, watery, slightly pink, sputum and became cyanotic. There was no aspiration of water, overhydration, vigorous exercise, inadequate thermal protection, or other obvious triggers to IPE.

Medical examination

There were widespread crepitations on auscultation, and her oxygen saturation on air was 88%. While breathing 50% oxygen, her partial pressure of oxygen in arterial blood (PaO_2) was 63 mmHg, with an oxygen saturation of 92%. A chest X-ray (CXR) showed pulmonary edema. Extensive cardiopulmonary investigations were negative, including electrocardiogram (ECG), transthoracic echocardiogram (TTE), stress test, histamine and hypertonic saline challenges. Other diving and non-diving explanations were excluded, and it was deduced that she suffered IPE. She returned to diver training and completed 50 dives without incident.

Comments

This case exemplified the concept of IPE occurring in a healthy diver.

CASE 3 (2004) [12]

A 52-year-old mildly obese female, an inexperienced snorkeler, was snorkeling off a tropical island. She was taking a beta-blocker and a calcium channel blocker for hypertension.

After 45 minutes, she tried to return 200 meters to shore, but was very fatigued and noted a bubbling in her chest. When she reached the shore she was dyspneic, with copious pink, frothy sputum; and cyanotic. On shore, she noted possible angina-type symptoms.

Medical examination

On hospitalization, the next day, she was much improved, but still had pulmonary edema and an oxygen saturation of 93%. Echocardiogram (ECG) revealed peaked T-waves in the lateral chest leads. Transthoracic echocardiogram (TTE) showed an area of inferolateral left ventricular wall hypokinesis and mild mitral regurgitation.

TTE two weeks later indicated that the left ventricular ejection fraction was reported as normal, with no evidence of regional dysfunction or mitral regurgitation. Cardiac isoenzymes and coronary angiography were normal.

Nine months later her hypertension was labile but persistent, and a right submandibular lump was noted. Dopamine levels were nine times normal. She underwent resection of a dopamine-secreting non-malignant right vagus paraganglioma. She was well on follow-up 14 years later.

Comments

Hypertension per se has been incriminated in IPE causation, as has the use of beta-blocker drugs [1,8,11]. The temporary TTE anomalies were consistent with SCM/TC; this is supported by excess dopamine production. This sympathomimetic action contributes to stress effects by significantly increasing heart muscle contraction force. Mitral regurgitation was evident soon after the incident, but not later.

Of note, the combination of a beta blocker and a calcium channel blocker is interesting, as this combination is usually contraindicated [13].

CASE 4 (2007) [14]

A 72-year-old male with a BMI of 25 kg/m^2 was a very experienced diver. He had a history of coronary artery disease (CAD), and a thallium stress test at age 63 showed exercise-induced myocardial ischemia of the lateral wall of the left ventricle. CAD was treated successfully by coronary artery bypass graft (CABG) at age 65, with no subsequent symptomatology and no significant abnormalities prior to the diving incident. The last stress ECG was normal, one month previously.

On the second day of a remote diving holiday, he performed a 50-minute multilevel dive to a maximum depth 15 msw, with a five-minute safety stop at 3-5 msw. The water temperature was 27°C, and there was a slight current. The dive was innocuous, without any excessive exertion. There were no rapid ascents, saltwater aspiration or other incidents.

At the safety stop he noticed increasing dyspnea, but, attributed this to a low-on-air situation or regulator resistance. He ascended and remained on the surface for about 10 minutes, during which time he had inflated his buoyancy compensation device (BCD) and adopted a head-out vertical position. He noted increasing difficulty in breathing from both his demand valve and his snorkel. He also observed the sensation of fluid crackling (rales, crepitations) in his lungs. He attempted to relieve the dyspnea by pulling on the neck of his tight wetsuit, without effect. Dyspnea, fatigue and the sounds of pulmonary fluid, cough and expectoration of frothy sputum were all aggravated by exertion, continued after he boarded the dive vessel, and then diminished over the next three hours.

After a 4.5-hour surface interval he felt normal and so dived again, on an almost identical profile and environment, but without any incident or difficulty. For this second dive he had dispensed with the tight wetsuit and original demand valve. The new regulator produced no excessive resistance to breathing. On surfacing, he assumed a horizontal position and breathed through his snorkel.

Subsequent clinical developments

After a five-year period of uneventful frequent snorkeling and scuba diving, he developed swimming-induced IPE (SIPE) on three separate occasions, all during moderate exertion snorkel swims. He subsequently developed angina of effort and effort-induced dyspnea, despite sestamibi CT scans and angiographic verification of well-functioning coronary grafts.

Resting TTE showed mild left ventricular hypertrophy (LVH) with normal cavity and function. A stress TTE showed hypokinesis of the inferior and septal walls, resulting in moderate systolic impairment. This segmental dysfunction improved during recovery. The TTE also demonstrated moderate aortic stenosis and mild mitral valve incompetence. The aortic stenosis subsequently became severe and ultimately required an aortic valve replacement.

Comments

This case allowed a comparison of different potential IPE contributors associated with almost identical dives, with both IPE and non-IPE consequences.

Scuba IPE was associated with previous cardiac pathology and coronary artery stenosis (corrected by CABG). Years later it developed again while snorkeling, with mild mitral incompetence and moderate aortic stenosis, but with no evidence of CAD. Moderate aortic stenosis and mild mitral incompetence may increase pulmonary vascular pressures, and this may be aggravated by exertion. Furthermore, challenges associated with immersion may cause mild mitral incompetence to worsen.

In the snorkeling IPE incidents, there were possible environmental contributors, such as exertion and head-out immersion.

CASE 5 (2007) [15]

A 45-year-old female was undertaking her fourth dive on a course. She did not disclose a history of migraine and adult-onset attention deficit disorder, for which she was taking 25-30 mg of dexamphetamine daily.

She was diving at a depth of 26 msw as part of Advanced Open Water training when she signaled that she was low on air, despite her gauge indicating a pressure of 120 bar. The instructor handed her his alternate regulator while he breathed from her regulator, finding no abnormality. She requested to surface; this was controlled by the instructor. She became progressively more dyspneic on ascent. Frothy sputum and vomit was evident when she reached the surface. Shortly afterward, she became unconscious and was towed to shore, where CPR was provided for an extended period but was unsuccessful. There was still 90 bar remaining in her tank.

Autopsy

The autopsy revealed pulmonary edema and post-mortem decompression artefact. The heart showed no structural pathology, but there was minor coronary artery disease, and the atria were dilated. On histology, the only significant finding was a fine patchy replacement fibrosis in the myocardium. There were equivocal signs of cerebral arterial gas embolism (CAGE) which may have been related to CPR.

Comments

The description of this event is highly suggestive of IPE at depth. The cause for this cannot be ascertained from the available evidence but the pre-existing presence of a left bundle-branch block (LBBB), atrial dilatation and sympathomimetic medication may have increased the risks of a dysrhythmia.

CASE 6 (2009)

This 63-year-old female had made more than 500 dives. She was taking proton pump inhibitors for reflux esophagitis, escitalopram for anxiety/depression, and hormone replacement therapy (HRT).

She suffered two separate IPE-related incidents while diving. On the first occasion, she made a dive in calm waters with a temperature of 19°C, completing an uneventful dive to 10.9 msw for 49 minutes. After a surface interval of one hour 47 minutes, she re-entered the water. By this time there was a slight swell and surface current. She was swamped by a wave and may have aspirated "a small amount of seawater" and coughed. During descent she felt short of breath and, on reaching 15.3 msw she remained breathless, despite stopping to slow and control her breathing. After swimming, she became more breathless and decided to abort the dive. She commenced a controlled ascent but shortened her 5-msw safety stop, as she was becoming increasingly dyspneic and incapacitated. The total dive time was 25 minutes.

When she surfaced, her buddy towed her to the dive boat. She was dragged onboard, as she was too weak to assist herself. She lay down and was provided with oxygen (O_2). She was gasping for breath, cyanotic and coughing up pink, frothy sputum.

Medical examination

She was evacuated to hospital by an air ambulance. On arrival, she was dyspneic, cyanotic and with reduced O_2 saturation (86%). CXR and computer tomography (CT) scan revealed evidence of pulmonary edema. Troponin level was elevated significantly. ECG showed abnormalities, including T-wave inversion. TTE showed an overall reduction in left ventricular ejection fraction to 53%, with global hypokinesis.

On the following morning she developed retrosternal chest pain extending to the left clavicle. Coronary artery angiogram was normal, with no evidence of ischemia. The TTE and ECG reverted to normal in a few days, on discharge, consistent with TC/SCM/TMD. Respiratory function tests (RFT) and provocative tests were normal. The final diagnosis was acute pulmonary edema, possibly aggravated by minimal saltwater aspiration and followed by myocardial damage. ECG, TTE and troponins were abnormal, but transitory. After much discussion she decided to continue with selective diving, against advice.

CASE 7 (2010) [Incident 2 of Case 6]

This now 64-year-old female had a previous incident of IPE, described above. She returned to diving. Five months later, after a nitrox course, a repeat diving medical examination, more dives and a tropical diving holiday, she experienced another, albeit milder, episode of IPE.

The conditions were less favorable – surface chop on a large swell, with a strong underwater current and a water temperature of 25°C. She descended to a depth of 30 msw, fighting the current and running short of air (down to 10 bar). On surfacing, she was exhausted and breathless. She was evacuated to hospital by air ambulance.

Medical examination

Oxygen was administered. CXR confirmed pulmonary edema. Blood O_2 saturation was reported to be reduced significantly. Echocardiography was undertaken the next day and was normal. A month later a cardiac MRI and lung function tests, including hypertonic saline provocation were conducted, again with normal results.

The patient returned to diving with restrictions that included appropriate thermal insulation, avoidance of exertion and a low tolerance to abort the dive if she became dyspneic. At the time of follow-up, she had completed approximately 100 further dives (in tropical waters) without incident.

Comments

This was a comparatively minor incident. It may have been aggravated by exertion, stress and increased inspiratory regulator resistance due to a low-on-air situation and resultant increased negative inspiratory pressure.

CASE 8 (2010) [16]

This 49-year-old woman was severely obese (BMI of 41 kg/m^2), with mild hypertension, hypercholesterolemia, anxiety and depression. She was taking paroxetine, alprazolam and levonorgestrel. She had been treated with diuretics for ankle edema and glyceryl trinitrate for possible angina.

Cardiac investigations showed no evidence of infarction. A thallium exercise ECG showed changes during maximal exercise and scan abnormalities were suggestive of reduced blood flow to the anterior wall of the left ventricle. The report stated that this could have been an artefact due to the overlying breast tissue. These changes were asymptomatic and normalized post exercise

She also suffered episodes of dyspnea on land, requiring hospitalization. Chest X-ray showed non-specific changes, and a CT pulmonary angiogram showed no evidence of pulmonary embolism or focal lung or pleural abnormality. She was subsequently prescribed salbutamol, although there was no definitive indication of asthma.

To improve her fitness, she enrolled in a diving course, but did not disclose the above information. During her

first open water dive, she waded for 70 meters, then surface-swam for a few minutes to reach a buoy 170 meters from shore. Wearing 17 kg of weights, she descended very briefly to about 0.5-1 msw before ascending and complaining of dyspnea and "feeling sick". She was observed to be breathing excessively and with a slight wheeze. She was towed to shallower water but was panicking. She coughed when a wave splashed over her face. She then requested salbutamol, which she self-administered four times. She soon deteriorated, became unresponsive and cyanotic with yellow, frothy sputum coming from her mouth. A defibrillator indicated pulseless electrical activity, rapidly decreasing to asystole. Resuscitation was continued for 30 minutes but the victim failed to respond.

Autopsy

Apart from pulmonary edema, there was no evidence of drowning or PBT. The main findings were of an enlarged heart and mild atherosclerosis of the coronary arteries. There were no features suggestive of arrhythmogenic cardiomyopathy. There was some mitral valve thickening of the anterior leaflet, with shortening and thickening of the papillary muscle (possibly mild mitral valve prolapse). Histology confirmed the fatty infiltration of the heart. The atrioventricular (AV) node showed mild muscular hypertrophy and myxoid change in some vessels, as well as in the mitral valve. There was no evidence of asthma.

Comments

Some chronic cardiac pathology was present, but not to a degree to cause death per se. A history of angina could have been a result of microvascular cardiac ischemia, as there was only minimal coronary artery atherosclerosis.

Dysrhythmias may have been a consequence of the undoubted psychological stress, extreme exertion by her standards, mitral valve disease and sympathomimetic drugs (especially salbutamol). Speculatively, these factors could also be contributory to SCM/TC, which is also consistent with the clinical history and the reduced blood flow to the anterior wall of the left ventricle.

CASE 9 (2010) [17,18]

This 51-year-old female was medically and physically fit, apart from childhood eczema and being overweight (BMI of 38 kg/m^2). She was a very experienced and well-qualified diver.

During a 30-meter surface swim against a moderate current she may have aspirated a small amount of seawater when she was swamped by a wave. She developed dyspnea as she rested at a marker buoy prior to descent.

She experienced progressive dyspnea and fatigue a few minutes after reaching 12 msw and aborted the dive. Cough supervened, together with copious pink sputum, wheezing and rattling sounds in the chest during respiration. Paramedics attended, and she was taken to hospital by ambulance.

Medical examination

On hospitalization, pulmonary edema and a transitory obstructive airways disorder were demonstrated. She responded quickly with O_2 and bronchodilators.

A month later the respiratory function tests, asthma provocation and cardiac assessments (including TTE and stress ECG) revealed no abnormality.

She was diagnosed with IPE. Although diving medical experts disagreed regarding her fitness to continue to dive, she did so and completed over 50 more dives uneventfully until her fatal dive, described below.

Comments

Exertion, and possibly aspiration, may have contributed to this IPE. Cardiopulmonary investigations revealed no evidence of chronic disease, although these follow up investigations were delayed and thus transient cardiac pathology such as SCM/TC would not have been detected. She conformed to the diagnosis of idiopathic IPE.

Case 10 (2011) [Incident 2 of Case 9] [17,18]

One year after suffering the IPE incident described above, and without any abnormality on extensive cardiorespiratory investigations, this now 52-year-old very experienced female diver undertook a night dive. After a 30-meter surface swim, she descended to a maximum depth of 18 msw. At 14 msw, and after 25 minutes she signaled her buddy to abort the dive. They re-traced their route and ascended slowly up the reef, the victim repeatedly indicating that she was "not OK." After 37 minutes when they reached the surface, she was dyspneic with cough, expectoration, an audible wheeze, and was incapacitated. She was towed 100 meters to shore, where CPR was performed, unsuccessfully.

Autopsy

The principal anatomical finding was pulmonary edema, with no additional evidence of drowning or PBT. Histological examination of the heart confirmed minor bridging of the left anterior descending (LAD)

coronary artery and showed interstitial hemorrhage and some associated contraction bands within the posterolateral left ventricle wall.

Comments

Moderate exertion may have contributed to the IPE. Resumption of diving after a previous IPE was controversial. Prompt investigations after the earlier incident may have allowed evaluation of a SCM/TC. Contraction band necrosis of the left ventricle myocardium at autopsy can have several causes, including SCM/TC [9].

CASE 11 (2011)

This 27-year-old female tourist was visiting a tropical island and undergoing her second day of an Open Water Diver course.

She had no relevant cardiorespiratory history. She was learning tasks at a maximum depth of 3 msw when she developed a tightness in her chest, difficulty in breathing, and a cough. She was adamant that she had not aspirated seawater (although she may have on the previous day). On surfacing, she developed more coughing and copious pink, frothy sputum.

Medical examination

A local physician recorded the presence of bilateral crepitations on auscultation.

Medical evacuation took several hours, during which she was given O_2 and improved so much that, apart from the CXR which supported the diagnosis of IPE, she was not subjected to cardiac investigations. She was discharged a day later.

Comments

Possibly due to the inadequate interrogation and investigation, no possible contributing factors were recorded. The water temperature was 28-29°C, and there was no excessive exertion required. Without further details she would be assessed as idiopathic IPE.

CASE 12 (2011)

This 59-year-old male had a history of childhood wheezing. He had a BMI of 30 kg/m^2 and hypertension (160/100 mmHg) for which he was taking an angiotensin II receptor antagonist and a beta blocker.

He was an experienced diver, using air and nitrox to a maximum depth of 35 msw. On three previous occasions he had experienced "shortness of breath" related to anxiety during a dive or on surfacing. He attributed this once to a "leaking regulator," but this was repaired and not evident in the other incidents.

He descended to a depth of 16-18 msw in unpleasant conditions, including cold weather, a water temperature of 11°C, surge and choppy surface conditions.

After about 20 minutes he noticed a sensation he described as "breathing wet" from his regulator, although he was certain that the regulator was not malfunctioning. He normally noticed a dry mouth while diving but not on this occasion (or on his previous three episodes of dyspnea). The visibility was poor, and he was feeling cold and anxious, so he decided to abort the dive and ascended with his buddy to the safety stop at 3-5 msw. While there, he noticed difficulty breathing so he decided to ascend after a dive time of 30 minutes. On surfacing, he experienced increased breathing difficulty and began to cough vigorously, expectorating white, frothy sputum with a pink tinge. He described a "rattling" in his chest when he coughed but did not notice a wheeze.

On the surface for about 10 minutes, he assumed a head-out vertical orientation, with BCD inflated. He remained very short of breath, with tightness in the chest and continuous coughing. Upon boarding the boat, he was observed to be cyanotic and was given O_2 via a demand valve. His difficulty in breathing eased after about 10 minutes.

Specifically, he did not notice any restriction to breathing from his regulator during the dive, no aspiration, and there was still approximately 100 bar cylinder pressure on completion of the dive.

Medical examination

In hospital, during the next few hours, he was given 100% O_2, and when this was occasionally withdrawn it was resumed due to a reduction in blood oxygen saturation (SaO_2).

Chest X-ray showed interstitial lung markings suggestive of pulmonary edema. Raised troponin levels (2.05 ug/L [normal < 0.05]) were consistent with recent myocardial damage. His ECG was initially normal, but later showed some ischemic changes, with widespread anterior T-wave changes. A coronary angiogram performed the next day was normal.

Cardiac catheterization revealed no critical coronary stenosis. The left ventricular end diastolic pressure was markedly elevated at 36 mmHg. There were segmental wall motion abnormalities consistent with stress-induced cardiomyopathy (takotsubo), with apical and distal inferior wall hypokinesis.

A TTE performed some days later, revealed normal left ventricle (LV) cavity size and systolic function, mild left ventricular hypertrophy (LVH) and inferoapical hypokinesis. There was mild thickening of the mitral and aortic valves, with mild aortic regurgitation and mildly elevated pulmonary artery pressure.

He performed 12 conservative dives in benign conditions over the following five years but has since given up diving.

Comments

IPE predisposing factors included treated hypertension, previous episodes of anxiety with diving and episodes of dyspnea with diving, possibly due to IPE. On this dive he developed IPE after deciding to abort due to cold and anxiety and while ascending.

Cardiac investigation revealed mild aortic and mitral valvular pathology and no significant coronary artery disease. There was elevation of troponin levels and evidence of left ventricular wall motion abnormalities which may have been pre-existing but which could also be consistent with a resolving acute TC/SCM/TMD. There was also post-event evidence of pulmonary hypertension and diastolic dysfunction which, if present pre-event, could have been predisposing factors as well.

CASE 13 (2011) [17]

This 55-year-old male had a past history of tightness in the chest, hypertension, dysrhythmias and tachycardias induced by exercise, and post-exercise syncope. Cardiological consultation and TTE 15 years earlier revealed a slightly thickened mitral valve leaflet. Cardiac consultations and TTE three years prior to the diving incident revealed mild aortic and mitral regurgitation with mild left atrial dilatation. Repeated cardiac assessments indicated no other significant structural abnormalities or evidence of coronary artery ischemia.

Despite his cardiac issues, he was physically very fit (BMI of 26 kg/m^2) cycling three times per week. He was undertaking physiotherapy for back pain and took diclofenac. He was a recently qualified, inexperienced diver with newly purchased gear.

He carried his own scuba gear 150 meters to the site without obvious cardiorespiratory problems or dyspnea, although his back was uncomfortable. The water temperature was 18°C, there was a mild surface current/chop, and visibility was less than 3 meters. With two companions, he descended to 4-5 msw. He repeated OK signals until, after four minutes, he signaled a need to surface. He did so with a companion. The ascent rate was described as "normal." Bloody fluid was observed coming from his nose. He indicated that he would return to shore by swimming under the pier to a ladder. A divemaster watched him from the landing. He was seen to float into view on the other side of the pier. His BCD was inflated, and he was floating on his back, unconscious. His head was above water, and his lips appeared cyanotic. Blood-stained frothy sputum was oozing from his mouth.

Rescue and retrieval were complicated, as they were unable to get him onto the landing. He was eventually towed to shore, where resuscitation was performed. The time from when he was first noticed to be unconscious and until CPR was commenced was eight to 10 minutes. He was cyanotic with fixed, dilated pupils. His airway was soiled with froth, vomit and water. Intubation and resuscitation were difficult with sputum and vomit present. The defibrillator indicated that the victim was in asystole and Advanced Life Support was implemented. After about 20 minutes there was return of spontaneous circulation (atrial fibrillation/AF).

Medical examination

He was transported to hospital. A CT brain scan was performed and reportedly demonstrated global hypoxic ischemia. Other relevant investigations included CXR. Pulmonary edema was evident as well as bilateral pleural effusions. A brain CT showed no gas emboli. He died several hours later.

Autopsy

The heart weight was normal but, the atria appeared dilated, and both ventricles were hypertrophic. The mitral valve showed thickening and myxoid degeneration of the anterior valve leaflet consistent with mitral valve prolapse. There was less than 10% narrowing of the LAD coronary artery. Histology of the heart showed mild to moderate perivascular and pericellular fibrosis and scattered microscopic subendocardial scars in the left ventricle. No contraction band necrosis was described.

The upper airways contained thin blood-stained fluid mixed with gastric contents. The lungs were heavy, congested and edematous. There was 150 mL of straw-colored fluid in the right pleural cavity and 100 mL in the left. There was an early aspiration pneumonia. No additional evidence of drowning or PBT was present.

Comments

IPE was a likely diagnosis. There was an absence of convincing evidence of cardiac ischemia. Pulmonary edema was severe, and the clinical deterioration with

ascent was consistent with this diagnosis. Mitral valve pathology with atrial dilation may also have contributed to IPE or to a fatal dysrhythmia.

The dive profile and autopsy essentially excludes PBT and decompression sickness (DCS) as initiating causes. The inflated BCD could have aggravated the dyspnea in the same manner as a tight wetsuit.

CASE 14 (2012)*

This 41-year-old female had no significant medical history and was on no medications. She engaged in moderate exercise and had a BMI of 25.2 kg/m^2. She was a moderately experienced air and nitrox diver, with a history of 47 dives. Her first incident was relatively innocuous, the second almost fatal.

Incident 1: During a dive to 28.4 msw for 21 minutes, she was relaxed and noticed no breathing difficulty or resistance to breathing during the dive. She felt fatigue on surfacing and complained of dyspnea and difficulty boarding the boat. She felt dizzy, with shortness of breath, a non-productive cough, subsequent weakness and difficulty with walking.

After a surface interval of approximately 2.5 hours she felt OK and made a dive to 9 msw for 27 minutes. The returning surface swim was in calm water for about 30 meters. She initially used a snorkel, but she developed shortness of breath, and she was much slower than the other swimmers. All symptoms resolved that day.

Incident 2: Three months later. She descended to 36 msw breathing Nitrox 30 for 17 minutes, in good conditions and a water temperature of 17°C. This was her deepest dive, and she was with her instructor. She possibly swallowed some water while on the surface prior to diving, as she was negatively buoyant due to a BCD problem that had caused some distress. She was breathing excessively and overexerting herself until at 15 msw her BCD problem was rectified, and she achieved neutral buoyancy. The next portion of the dive was uneventful: She was swimming well and without any distress. However, at around 12 minutes into the dive and after two to three minutes at the maximum depth, she noted a "fuzzy light-headedness" and wanted to ascend. At 15 msw she had to stop to "catch her breath." She again indicated that she wished to surface, which she did in a diagonal slow ascent. She recalls a "choking sensation" on inhalation. Her companion held her and controlled the ascent, bypassing the safety stop. He noticed a dark fluid from her mouthpiece at about the 7-msw depth. On surfacing she coughed and expectorated pink, frothy sputum. She was unable to inform her buddy that she could not breathe.

She has no memory of the subsequent rescue, but the instructor stated that there was no aspiration during this time. She was hauled onto the boat, unconscious, although breathing weakly, placed into the recovery position and received O_2 via a non-rebreather mask. After a few minutes of O_2 breathing, she began to breathe more easily and became responsive, despite producing large quantities of pink, frothy sputum.

Subsequent testing of the regulator revealed no source of leakage or water entry from the second stage, but there was a possible first stage problem, with the high-pressure seat housing cap which may have reduced the flow volume at some pressures. At no stage was this evident during testing, but could theoretically have resulted in negative-pressure inhalation.

Medical examination

She was evacuated to the nearest hyperbaric unit for assessment. The doctors concluded that recompression was not required, and she was admitted for management of suspected IPE. After about two hours on O_2 and CPAP, her breathing became much easier.

A CXR demonstrated pulmonary edema, which was partly resolved on discharge and normal on the third day. Substantially elevated troponins were noted on admission (182 ng/L) (decreasing to 126 ng/L on day of admission), with leukocytosis of 18,220, 92% neutrophils. Respiratory function testing revealed a forced expiratory volume (FEV) 1.0 / forced vital capacity (FVC) 65%/63% of predicted levels during hospitalization. A month later, the results were 80%/90% predicted.

Specialist cardiac assessment a month later, which included ECG, stress test and TTE, revealed a first-degree and right bundle-branch block (BBB), and a workload of 13.4 METS without any abnormality of valvular action, ventricular function, wall thickness or ischemia.

She subsequently performed two problem-free dives to 10 msw but has since decided to stop diving for fear of a recurrence.

Comments

Higher-than-normal O_2 partial pressures (e.g., as seen with nitrox) have been implicated in IPE [19], although some physiological evidence suggests that this is unlikely [20,21].

*Although this diver had two likely incidents of IPE, it is only recorded as a single case as there was no medical assessment and diagnosis following the first incident.

Excessive negative buoyancy, anxiety and exertion may have contributed to the second incident. High troponin levels are often associated with transient myocardial damage. As formal cardiological assessment was delayed a month, the normal findings are not incompatible with a TC/SCM/TMD diagnosis. Both IPE instances were aggravated by ascent to the surface. Regulator problems may have increased negative inspiratory pressures.

CASE 15 (2012)

A 50-year-old diver with a history of 90 dives was fit and involved in a variety of physical sports. He had no significant medical history.

He performed a boat dive, with a water temperature of 13°C, wearing a drysuit and reported feeling warm and comfortable. His regulator had been serviced recently.

On the first dive of the day he went directly to 37 msw before working up to 20 msw. There was a very strong current; he was working hard, using a lot of air. He was low on air at the safety stop, so he changed to his pony bottle and surfaced. He had not noticed any significant breathing resistance from either regulator used.

After a three-hour surface interval, during which he felt fine, he made another dive to 30 msw, working up the reef to 25 msw. At this point, he noticed that he "did not feel right." He decided to ascend; at about 10 msw his breathing became labored. Thinking this was likely due to his regulator, he changed to his pony bottle, but this made no difference. He ascended to the safety stop at 5 msw. After a few minutes there, he decided to terminate the dive, as breathing had become too strenuous. On surfacing, he found it extremely difficult to breathe. He needed assistance to board the boat and was weak, breathless, wheezing and coughing up pink, frothy sputum. Once on the boat, the crew removed his drysuit and he was given O_2. He was evacuated to hospital by air ambulance.

Medical examination

In hospital he received O_2 and CPAP and improved substantially over one hour. His SaO_2 was 88% on air.

The CXR showed pulmonary edema. Initial cardiac examinations were normal. ECG showed sinus tachycardia with no evidence of ischemia. Troponins levels were not measured.

Cardiac assessment six weeks later revealed repeated ventricular ectopic rhythms on ECG, mild concentric left ventricular hypertrophy on TTE, together with borderline biatrial dilatation.

The victim ceased diving and swimming but engages in regular, energetic cycling and has had no subsequent medical issues over the six years since the IPE incident.

Comments

Negative-pressure inhalation was possible in the first dive, due to a low-on-air situation. Both dives were physically demanding, against currents.

Apart from these possible provoking factors, this case is consistent with idiopathic IPE.

CASE 16 (2012) [22]

A 58-year-old male nurse had a past history of anxiety and depression, reflux esophagitis, paroxysmal atrial fibrillation (AF) and shoulder pain. He was obese (BMI of 38.1 kg/m^2). He was reported to have been non-compliant with his AF medications and had four emergency department admissions over the previous seven years, on one occasion requiring cardioversion. His AF appeared to be occurring more frequently.

He suffered multiple episodes of palpitations with durations from one to six hours. His cardiologist had reportedly recommended a pacemaker, but no device had been fitted. His medications were esomeprazole, ibuprofen, metoprolol and tadalafil, with amiodarone being suspended. He was also taking analgesics for shoulder pain.

He was previously an experienced diver but had not been diving for 20 years until recently participating in some shallow river and shore dives. On the diving medical questionnaire, he failed to declare his cardiac conditions. He participated in three uneventful shallow dives.

On the first "deep dive" of the course, he breathed nitrox with 32% O_2. Conditions were fine, and the water temperature was 16°C.

After about 10 minutes at 30 msw, during which diving skills were assessed, the group ascended to 20 msw for additional tasks. On further ascent to 14 msw the victim lagged and signaled that he was out of air and wished to ascend, despite his contents gauge reading 130 bar. He then ascended quickly in a prone position. On the surface, he was unconscious, floating facedown with his regulator out. He was "bubbling and foaming a brownish liquid from his mouth." CPR was attempted but was unsuccessful. Gurgling sounds were heard with each rescue breath. His dive equipment was found to be in good condition and fully serviceable.

Autopsy

Pulmonary edema was present. There was no additional evidence of drowning, PBT or DCS. The heart weighed 506 g (n = 331–469 g) with a globose shape and dilation of the right atrium and both ventricles. There was a 30% stenosis of the left anterior descending coronary artery. Histology of the heart showed mild patchy subendocardial and perivascular fibrosis and myocyte hypertrophy but no acute ischemic changes.

Comments

The IPE was likely associated with a cardiac etiology. A history of clinically uncontrolled paroxysmal atrial fibrillation was probably significant as the immersion-related challenge could have triggered further AF. The resultant hemodynamic effects, possibly influenced by the multiple cardiac drugs, including beta blockers, may have aggravated pulmonary edema.

CASE 17 (2013)

A 61-year-old female had no previous medical history but was found to have a left BBB detected on an ECG performed during workup for cosmetic surgery several years earlier.

After 12 previous uneventful dives, she completed one dive to 22 msw for 35 minutes, took a surface interval of 90 minutes, then made a 19-msw dive for 24 minutes in warm tropical waters off a remote island. The current was strong, and after 10 minutes she began to have trouble breathing. She had 120 bar of air remaining. She started to panic at depth, realizing that she could not continue the dive, and began to ascend, controlled by her companion.

Upon surfacing, she was totally incapacitated and needed to be rescued onto the boat. There she was semiconscious "unable to get enough air." She then lapsed into unconsciousness for about 45 minutes, during which time she was gasping and coughing up fluid and variously "white, yellow and pinkish foam." She became apneic for about a minute until she was administered rescue breathing and given supplemental O_2. She then became tachypneic and tachycardic.

She was evacuated by boat and vehicle to a local clinic. At that stage she remained on O_2 and her breathing settled. Subsequently, well after the incident, she thought that she might have breathed in some water around the mouthpiece when she started to panic.

Medical examination

This was cursory, and no more information was available. She has not pursued further diving but has snorkeled in tropical waters without incident. She has reported no subsequent medical events.

Comments

Overexertion was noted, as were anxiety/panic, all risk factors for TC/SCM/TMD syndromes. However, without echocardiogram or troponin evidence, such diagnoses are speculative. There was no evidence of previous cardiac illness, except for left BBB. A history of some aspiration of seawater was proposed, but this was in retrospect and not reported at the time.

Without definite evidence, this case may be included as an idiopathic IPE, although other possible causes could be considered.

CASE 18 (2013)

This 52-year-old man with a BMI of 29 kg/m^2 was physically very fit, but with factor V Leiden deficiency and asymptomatic non-Hodgkins lymphoma. A recently qualified diver, he routinely coughed on surfacing after dives. He performed two dives to a maximum depth of 24 msw, each for 22 minutes. He coughed a little on exiting the first dive. Neither dive involved exertion, and he did not aspirate water.

He was about to leave the bottom during the second dive when he started to cough. His tank pressure was 60 bar, but there was no noticeable resistance to breathing. He ascended to a 4-msw safety stop when coughing became continuous. He surfaced and managed to board the boat with assistance, and while coughing up pink frothy sputum. He then improved rapidly.

Medical examination

On examination in hospital his SaO_2 was 83%; he was given supplemental O_2. Apart from a slight cough, he was asymptomatic the next day. CXR verified pulmonary edema. TTE and ECG were normal. There was a slight elevation in troponin levels.

A month later his RFT and expiratory spirometry were normal or above predicted levels. Five months after the incident a cardiac assessment showed normal ECG, exercise stress ECG, and exercise TTE.

He has subsequently made several shallow, exertion-free dives without incident.

Comments

Apart from immersion, no likely contributing factors were elicited. The small troponin increase was not explained. It could imply a possible cardiac involvement, although it does occur in settings other than cardiac ischemia secondary to coronary artery disease, and has been reported frequently in cases of IPE [23]. Otherwise, this case conforms to idiopathic IPE and was so designated.

CASE 19 (2013)

This experienced diver was 57 years old, with atrial fibrillation and a history of transient ischemic attacks for which he was anticoagulated on rivaroxaban. On the fourth day of a diving holiday, he was using a Pelagian rebreather (Rebreather Lab, Thailand, 2010) with back-mounted counterlungs. Because of leg cramps, he took extra electrolyte and fluid supplements pre-dive.

The plan was for a 180-minute cave dive with a maximum depth of 13 msw and an average depth of 4 msw. He felt he was struggling with his breathing at times and at about 56 minutes he realized he would not complete the dive plan. After a dive time of 75 minutes he was exhausted and faint and was sucking the mask onto his face uncontrollably during inspiration. He felt his breathing was difficult and that he was not getting enough air. He converted to open-circuit and felt better, breathing well. He then reverted to the closed-circuit rebreather (CCR) without further difficulty.

On surfacing, he noted a small blob of a light pink substance from his mouth. With every breath, he noticed a "gurgling sound and feeling in his chest." On the boat he had difficulty climbing the steps and had problems breathing. He improved after 15-20 minutes.

Medical examination

A diving doctor suggested a carbon dioxide toxicity with possible IPE. The next day he had a CXR, which showed a small amount of congestion indicative of pulmonary edema, and a normal ECG. Pulmonary crepitations were heard.

He discontinued diving for several years but remained enthusiastic. He returned to some relatively basic diving and snorkeling, completing around 30 uneventful dives in good conditions. Four years after his incident, a TTE showed mitral sclerosis and mild mitral incompetence, mild pulmonic regurgitation with normal pulmonary artery pressures. A stress ECG showed atrial fibrillation with a controlled ventricular response. There was no evidence of cardiac ischemia.

Comments

It is possible that the initial symptoms were due to hypercapnia, as diagnosed. Negative inhalation pressures may have been caused or exacerbated by the back-mounted counterlung and the minimal increased density by breathing gases at depth. Negative static lung load itself could predispose to IPE by augmenting intrapulmonary blood volume.

TTE demonstrated mitral valve sclerosis and regurgitation, which would be expected to have increased pulmonary venous pressure. Closed-circuit rebreather (CCR) units commonly run with a partial pressure of oxygen (PPO_2) of 1.3 ATA, which may be expected to result in a reduction in pulmonary arterial resistance. This, associated with increased venous pressure, overhydration and negative inhalation pressure as described above as well as the presence of atrial fibrillation may have tipped this otherwise reasonably fit (11-MET fitness test) man into pulmonary edema. It is of interest that the individual received some symptomatic relief when he switched to open-circuit, which would have both reduced the negative inspiratory pressure and the PPO_2.

The relatively unimpressive CXR may be explained by the investigation being done the day after the subject was asymptomatic.

CASE 20 (2014) [6]

This 56-year-old female was fit and healthy, except for an incident of chest tightness and dyspnea for a few days 10 months previously. This was investigated, but no cardiac anomaly was found. She also had a couple of episodes of shortness of breath on strenuous exertion, which were not investigated. She took no medications, and her BMI was 25 kg/m^2.

She had minimal snorkeling experience. The water temperature was 15-16°C, but she was wearing a wetsuit as she swam among dolphins. During the third swim she complained that she could not breathe, and began to cough, expectorating copious frothy sputum. She continued to deteriorate after being rescued into the safety boat and was very weak, cyanotic and vomiting before becoming unconscious. She died soon after hospitalization.

Autopsy

This verified the pulmonary edema and noted cardiomegaly, but no evidence of cardiac ischemia. There was no additional evidence of drowning.

Comments

Cold-water exposure may have contributed, but this is countered by the use of a wetsuit and the absence of depth exposure. Stress is likely, because of inexperience in snorkeling and the exertion required.

The patient had previously experienced repeated incidents of exertional dyspnea, which could have indicated a temporary cardiac anomaly such as dysrhythmia or TC/SCM/TMD, or more simply a lack of adequate physical fitness for the exertion undertaken. Cardiomegaly implies some cardiovascular pathology.

CASE 21 (2015) [24]

This 67-year-old female was a very experienced air/nitrox diver (>1,800 dives over 12 years), usually diving in warm tropical waters and sometimes against strong currents.

She had no cardiac or respiratory problems. Her BMI was 21 kg/m^2 and she took pregabalin for orthopedic problems, rosuvastatin for hypercholesterolemia and esomeprazole for possible gastric reflux. Six months previously, she had a cardiac CT calcium score of 100 (normal). Hypercholesterolemia was well controlled. Transthoracic stress echocardiography was normal.

She went diving in gentle conditions; mild current, good visibility, and a temp of 19°C. She wore an additional wetsuit vest, as she had been cold while diving the previous day. The additional buoyancy necessitated a head-down descent.

The dive was uneventful, until at 15 minutes and at the maximum depth of 20 msw, when she became aware of "not feeling right" and a slight difficulty in breathing. She indicated that she wanted to ascend, which they did slowly over eight minutes, to the 5-6 msw mark for a five-minute safety stop. There, the dyspnea increased, and they ascended to the surface. She became increasingly short of breath, started coughing and expectorating pink, frothy sputum. She felt a rattling sensation in the chest. She was assisted onto the boat, laid supine and administered high-concentration O_2. She was evacuated to hospital by helicopter.

Medical examination

A diagnosis of acute pulmonary edema was made, and chest crepitations were noted.

A CXR verified the diagnosis of pulmonary edema, with reduced SaO_2. Troponin T levels were markedly elevated to 4,052 ng/L. The ECG showed premature ventricular complexes, left axis deviation and non-specific T-wave abnormalities on lateral leads. A TTE (one hour after admission) showed moderate segmental impairment of systolic function, a left ventricular ejection fraction (LVEF) of 38% and extensive anterolateral, lateral and posterior hypokinesis with mild mitral incompetence. Coronary angiogram (within hours of admission) revealed moderate segmental LV dysfunction (mid-anterior-lateral and inferoposterior hypokinesis with sparing of the apical and basal walls) with only mild diffuse coronary artery disease, not requiring any intervention.

Treatment consisted of 100% O_2, CPAP, diuretics, aspirin and clopidogrel. She was well, without the need for further treatment, after six hours.

A repeat TTE (six days later) showed normal LV and RV size and function; LVEF 62%; Grade 1 (abnormal relaxation) diastolic dysfunction with normal estimated filling pressures; normal estimated R heart pressures (RVSP = 34%); mild (grade ¼) mitral and tricuspid regurgitation. LFT was normal and there were no subsequent abnormal cardiological investigations, or symptomatology.

With the above findings a diagnosis of IPE with takotsubo cardiomyopathy was made.

Comments

She did not consider this to be a stressful dive. There was no excessive resistance to breathing through the regulator. There was no aspiration of seawater and no bubbling sensation in the second-stage regulator. The wetsuit was not overtight. She had no previous or subsequent cardiorespiratory problems. The dive history all but excluded dysbaric illnesses and aspiration, and air consumption (12.4 L.min^{-1}), validated her denial of "stress".

Clinical symptoms and radiology were consistent with IPE. Apparent aggravation during ascent may have simply reflected the natural progression of the problem or worsening of hypoxia as the inspired PO_2 fell. The transiently abnormal cardiac investigations indicated a TC/SCM/TMD, which may have been the cause of the event, although it is possible that TC was precipitated by IPE developing from other causes. There were no predisposing factors other than immersion.

CASE 22 (2015)

This 36-year-old male was a very experienced technical diver, self-described as "somewhat obese" and with hypertension. He was diving overseas, in water temperature of around 4°C, using a CCR. He had overhydrated in an attempt to prevent decompression sickness.

He descended to a depth of 70 meters of fresh water (mfw) before a short 'bounce' to 87 mfw for a few minutes. On returning to 70 mfw, he was aware of difficulty in

breathing and decided to terminate the dive. During ascent he developed coughing into his equipment. He was very dyspneic, exhausted and distressed on surfacing, with a wheeze and a crackling sound in his lungs. His sputum was copious and frothy. He had carried out appropriate decompression, including breathing 100% O_2 from 6 mfw to the surface.

He breathed surface O_2 for four hours, during which time his symptoms improved, becoming asymptomatic after six hours. Decompression sickness was dismissed by the diving medical expert consulted, as symptoms developed at almost maximum depth.

Medical examination

A delayed cardiological assessment was unremarkable apart from hypertension, which was treated.

During a six month layoff, he attended to his obesity and undertook training to improve his physical fitness. He then resumed his diving activities, against medical advice, but not in such cold water and without overhydration. He has performed more than 100 dives without recurrence of problems.

Comments

This case illustrates the possible contributions of immersion, hypertension, cold exposure and overhydration.

CASE 23 (2015)

This 58-year-old female diver (BMI of 27 kg/m^2) had a double mastectomy, hysterectomy, retinal detachments, a right knee replacement and two, small below-knee DVTs, all some years previously. For a month prior to the current diving incidents, she experienced considerable stress.

She had made 3,500 dives over 35 years, including deep and some technical diving, and had experienced two possible episodes of DCS (one aviation-induced). On this occasion, she was on an overseas trip and had arranged some diving. She wore a hired drysuit and 11 kg of weights. On the first day, she had a problem-free dive in a freshwater stream (-1°C).

The next day, she made a dive to 20 meters for 30 minutes on a hydrothermal vent. The sea was very calm with no current, and the water temperature was -1°C. The gradual descent took about 10 minutes, as did the ascent to the safety stop. However, halfway through the dive, the drysuit leaked. She was getting wet and feeling colder but persevered. No other issues were evident. She stated that she did not feel nervous or worried. Toward the end of the safety stop, she developed difficulty breathing, taking rapid, shallow breaths. The symptoms appeared when she was in a head-up, vertical position during the ascent.

Upon surfacing, she was unable to remove her gear to board the boat and required assistance. She developed some coughing but did not observe the nature of the sputum. She then vomited. She felt cold and needed to be warmed. She felt weak and noticed crackling sounds in her chest – more on the left side – and a sensation of wheezing for about 10 minutes. All symptoms resolved after about an hour.

The second incident occurred three days later at the same site. The water temperature was again -1°C; conditions were calm with no current. The dive was to 14 msw for 30 minutes in duration, with slow descent and ascent. The suit remained dry, and the dive appeared to be problem-free until, at about 3 msw near the end of the dive, she suffered the same sensation of breathlessness and associated symptoms as previously described. The symptoms developed when she was in a head-up vertical position, during the ascent.

This was more incapacitating than the first incident, with the diver being rescued and towed to the boat. The chest symptoms were bilateral; she felt weaker and required assistance. She was offered O_2, which she rejected, and she spat out some fluid during the walk to the car. She did not feel well the following day but did not seek medical attention, although some chest tightness persisted.

Medical examination

Medical assessment and cardiological consultations and investigations were performed the following week when she had returned home.

She had mild hypertension and hypercholesterolemia. The initial ECG revealed atrial extrasystoles and ischemic ST-T changes in lateral leads. Repeat ECG showed sinus rhythm with inverted T waves in V3-6. ECG a week later, when the patient was asymptomatic, revealed sinus rhythm with a first degree AV block and ischemic ST-T changes in the anterolateral leads.

A TTE indicated that the LV was of normal size, although there was mild segmental impairment of the left ventricular systemic function, with hypokinesis of the distal anterolateral wall and, more prominently, of the distal anterior wall. There was further hypokinesis of the mid- to distal inferolateral wall and inferolateral aspect of the apex. There was impaired diastolic function, an ejection fraction of 50%, and the left atrium (LA) was mildly

dilated. Troponin was 276, 219 and 144 ng/L on consecutive days, and 17 three weeks later (n < 16). Coronary angiogram, chest CT and cardiac MRI were then normal.

She was treated with statins over the following few weeks, but side effects required these to be suspended. TTE a month later showed sinus rhythm and normal left biventricular size and function. Left ejection fraction was 73%, valvular function was normal, and there were no segmental wall motion abnormalities.

Further follow-up three months later confirmed a normal ECG. The TTE indicated that LV systolic function had completely normalized, and there was no significant valvular abnormality. There was mild left atrial dilatation and impaired diastolic function.

The cardiologist diagnosed takotsubo cardiomyopathy.

Comments

Takotsubo cardiomyopathy was diagnosed, based on the atypical echocardiographic findings (which reversed over the following weeks), abnormal ECG findings (that also reversed over this time), troponin levels that were still high, but reducing, when tested nine to 11 days post incident, and the absence of coronary artery ischemia on investigation. Although TC may have been the cause of IPE, it is also possible that it was precipitated by IPE developing from other causes.

CASE 24 (circa 2015)[25]

A 21-year-old medically and physically fit trainee military diver was exposed to maximal exertion, including an extremely strenuous 2-km ocean swim in tropical water of 30°C. To avoid dehydration, he had consumed 500-1,000 mL of water prior to the swim. In the 30 minutes post-swim, he complained of dyspnea and chest tightness, cough and blood-stained sputum. There was no history of aspiration. He was promptly examined by the attending medical officer.

Medical examination

Over the next two hours his O_2 saturation was 90% and he was given supplementary O_2. A CXR showed bilateral perihilar congestion with air space opacities in the right lower lobe and retrocardiac region, indicating pulmonary edema. His ECGs were normal, as was the heart, radiologically. Cardiac enzymes were normal, but creatine kinase was elevated, possibly related to some mild rhabdomyolysis. Renal and cardiac investigations were negative, including hematological and biochemical screenings.

Over the next two days, he remained afebrile and became clinically well, with CXR and muscle enzymes reverting to normal. He resumed military diver training without incident.

Comments

This case was typical of the swimming-induced pulmonary edema (SIPE) described in healthy military/combat swimmers and triathletes [26,27]. The diagnosis was SIPE aggravated by extreme aquatic exertion (exercise-induced IPE), and possibly overhydration.

CASE 25 (2016)

This female diver was aged 51 years and had a BMI of 35.5 kg/m^2. She gave a history of no significant illnesses, apart from currently experiencing menopause. Her comprehensive diving medical revealed moderate hypertension, possibly related to recent and significant social stress. She had a normal ECG, a normal stress ECG with a Bruce protocol to 9.5 minutes, without issue. A stress TTE showed normal wall motion at rest with all segments hyperdynamic immediately post exercise. There was no evidence of cardiac ischemia.

She engaged in snorkeling on a regular basis, without difficulty and a day earlier had commenced her Open Water Scuba course, with pool and initial open water dive to a maximum of 10 meters, without incident. On the second day, she attempted her second open water dive. Prior to the dive, she noticed palpitations and a "racing" heart rate, which occurred when walking 100 meters to the dive site. She felt very agitated in the water before descent, while in the head-out position. Following a 10-meter swim, she descended to 1 msw depth, when she was distressed by tachycardia, wheezing and rattling in her chest, aggravated by respiration.

She had no exposure to cold, and she was wearing both a wetsuit and a thermal vest. The wetsuit was not excessively tight. Initially no resistance to breathing was observed, no removal of the regulator took place, and there was no aspiration of seawater.

She decided to ascend and after discussion with her diving instructor she rested on the surface for around six minute, during which time her instructor also noted she had a rattling sound with respiration. They decided to descend to a depth of 6 msw to conduct dive exercises. Before she reached this depth, probably around 5 msw, her heart was racing, and the rattling sensation was more evident. She requested ascent and they did so. She then required help in returning to the beach and in removing some of her diving equipment.

During the return 100-meter walk up the beach, she had respiratory distress, including the rattling inspirations and about 10 episodes of coughing and expectoration of blood-tinged (bright red and then becoming pink) sputum. She commenced O_2 breathing at 10-15 minutes after the dive. Dyspnea and inspiratory rattling was noted by all observers. An ambulance was requested, and she was transported to hospital. A subsequent check on the performance of the regulator revealed no obvious abnormalities.

Medical examination

In the ambulance, her SaO_2 was 88% on air; she appeared pale and lethargic, with ongoing blood-stained, frothy sputum. She was admitted to hospital where she remained on O_2 and was largely asymptomatic in less than an hour.

A CXR demonstrated pulmonary edema. Initial troponin T was elevated at 127 ng/L, reducing the next day to 81 ng/L. TTE revealed a LV of normal size and systolic function, borderline concentric LVH, borderline LA dilatation, raised PA systolic pressure of 45 mmHg and mild tricuspid regurgitation.

A follow-up CT coronary angiogram showed normal coronary arteries and a zero-calcium score. A Holter monitor revealed no abnormalities apart from infrequent atrial and ventricular ectopic beats. On subsequent examinations the only anomaly observed was a BP of 148/100. An ECG was normal with sinus rhythm and a TTE showed normal systolic function and no valvular abnormality. Her pulmonary artery pressure had returned to normal.

She was advised not to dive and to avoid snorkeling as well. The provisional diagnosis was IPE and reversible myocardial dysfunction (RMD).

Comments

This was a middle-aged, healthy female who experienced IPE with evidence of a mild reversible myocardial injury. Other than the association of IPE with hypertension there were no obvious causes.

CASE 26 (2016)

A 63-year-old very experienced male diver was diving alone in a protected, shallow bay. After an hour he surfaced and was seen waving an emergency glow stick and heard screaming for help. Lifesavers from an adjoining beach reached him with a rescue board. They conversed with him as they removed some of his equipment. He became cyanotic and unconscious and died during the 10-minute ride to the life savers' clubhouse.

Autopsy

This revealed pulmonary edema in an obese (BMI of 34 kg/m^2) male. There was no additional evidence of drowning or PBT.

Other relevant findings included asymmetrical cardiac hypertrophy affecting the left ventricle and interventricular septum, with non-specific features affecting the heart muscle. The coronary arteries were patent, and there was no evidence of ischemia. Histological examination of the heart muscle showed non-specific features which may be associated with systemic hypertension.

Histologically there was marked myocyte hypertrophy of the left ventricle, with focal areas of subendocardial replacement fibrosis. There was also increased perivascular fibrosis. An adrenal adenoma was found.

Comments

While the changes in the lungs could have arisen from several causes, the pathologist suggested that IPE must be considered as a likely cause.

CASE 27 (circa 2016) [28]

This 58-year-old male was a very experienced scuba diving instructor. He had been diagnosed with moderate mitral valve incompetence, but his diving was not restricted. There was a possible history of an asthmatic reaction with a respiratory infection.

Six months after the mitral valve diagnosis, he noticed dyspnea and cough after swimming exertion. This cleared and two days later he made a dive to 18.7 msw for 56 minutes in water of over 20°C. The dive included a 5-msw safety stop, where he breathed 100% O_2 as a training exercise. After he resumed his ascent, he developed severe dyspnea that worsened when he surfaced. He removed his wetsuit, which felt tight, and resumed breathing 100% O_2. Despite this, he developed a cough and then hemoptysis.

Medical examination

He was hospitalized; his SaO_2 read 96%, on O_2. The CXR and CT scan demonstrated pulmonary edema.

The pulmonary manifestations continued despite the administration of O_2 and antibiotic treatment and remained present for five days. He received three hyperbaric treatments to exclude decompression illness. This complicated the clinical presentation, as did the development of a pyrexia of 39°C.

Apart from raised C-reactive protein and B-type natriuretic peptide (BNP) results, there were no other manifestations suggestive of a community-based pneumonia, DCS or PBT. All other investigations were normal. The mitral valve incompetence was verified.

Echocardiograms performed after recovery demonstrated severe mitral valve regurgitation, which was treated surgically with a mitral valve replacement.

Comments

This case report's uniqueness lies in the protracted nature of pulmonary symptoms beyond the anticipated duration of IPE once the victim was rescued.

Mitral valve incompetence can result in both increased pulmonary vascular pressures and pulmonary edema [29]. Therefore, it may also be a contributor to the development of IPE. However, the duration of pulmonary edema in this case seems exceptional and may be influenced by the severe mitral regurgitation. Where this is due to annular dilation, LA loading such as occurs with immersion may result in acute aggravation of the regurgitation.

The pulmonary symptoms experienced two days before the major IPE incident could well be either swimming-induced IPE, or the development of pulmonary infection, subsequently treated by antibiotics. Pulmonary infection supervening on IPE could also be an explanation for the prolongation of symptoms.

The tight sensation from the wetsuit could be either a contributing factor to IPE or merely an aggravator to the IPE symptoms.

CASE 28 (2017)

This 61-year-old female was overweight with non-insulin dependent diabetes, but no longer taking medication and with no known complications. Her diving medical examiner advised against diving.

On her first open water scuba dive, she donned her equipment, including 8.1 kg of weights, and walked slowly but with breathlessness 50 meters to the beach. She complained that her wetsuit felt too tight. Conditions were "ideal," and the water temperature was 20°C.

The maximum depth at the site was 8 msw; average depth during the dive 4.2 msw. After 30 minutes, and at a depth of 4 msw, she grabbed her instructor and spat out her regulator. The instructor immediately purged her regulator and replaced it. She was wide-eyed, breathing rapidly and shallowly. She clutched her throat before becoming unconscious.

The instructor controlled their ascent and towed her 30-50 meters to shore, with her head being supported out of the water by another diver. The instructor was confident that she had little opportunity to aspirate water. She had white, frothy sputum coming from her mouth. She became unconscious and apneic.

Trained lifesavers were available, and an AED was attached within 10-15 minutes of the incident, but no shock was advised. Continued resuscitation and transfer to a nearby hospital resulted in return of spontaneous circulation after prolonged asystole.

Medical examination

A coronary angiogram was unremarkable. A ventriculogram, showed moderate segmental systolic dysfunction with good basal and apical function, but hypokinesia of mid-anterior and inferior walls. Troponin rose from 25 ng/L on arrival at hospital to 540 ng/L ($n < 16$).

She failed to respond to treatment and died six days later. The autopsy revealed focal contraction bands in the LV, mild thickening of the LV (14 mm) and focal moderate CAD up to 50-70%. There was evident organizing bronchopneumonia and cerebral edema with ischemic changes.

Comments

Ventricular dysfunction was demonstrated; however, its significance after prolonged asystolic arrest and CPR is unclear. The history of excessive exertion for her limited physical capability, and probable anxiety/panic some 30 minutes into the dive is suggestive of an acute underwater event. A TC/SMC/TMD explanation for her IPE is possible, with the pathology in the mid-ventricular region [30], but it is not possible to determine whether these cardiac changes contributed to the IPE event, or were a consequence of myocardial injury during her cardiac arrest. A tight wetsuit could have aggravated the situation.

CASE 29 (2017)

This female diver aged 55 years (BMI of 25.8 kg/m^2) was in good health and physically fit, doing competitive long-distance swimming and regular fitness training. Two years earlier, she was investigated by a cardiologist for weakness and dizziness; it was observed that she had a low pulse rate. However, ECG, stress TTE and Holter monitor readings were normal. At age 38 her brother had suffered from dysrhythmias, paroxysmal atrial fibrillation (PAF). He experienced five such episodes that required electrical cardiac reversion to restore sinus rhythm.

She had made 55 previous dives, all incident-free and mainly in tropical waters. On this occasion, the water temperature was 6–10°C. She was not cold, due to the effective wetsuit she wore, although she had to carry 17 kg of weights to compensate for this. She was anxious for her less experienced buddy diver, her daughter.

They descended to 10-15 msw. She was slightly negatively buoyant. After 10 minutes her daughter indicated that she wanted to ascend. The victim found it harder than expected and, at about 8 msw, began to breathe hard, causing her to feel more anxious. On surfacing she was cyanotic, and her breathing was "wet, rattly and wheezy." On reaching shore, she was very weak, wheezing and coughing frothy, pink sputum. She felt some relief by kneeling on all fours, but not by lying supine. She was evacuated to hospital.

Later review of the equipment revealed an air consumption of 84 bar in the 14-minute dive, greater than was customary for her.

Medical examination

She received relief of her symptoms within one to two hours by breathing O_2, but signs of pulmonary edema persisted for several more hours. These resolved with O_2 and bilevel positive airway pressure (BiPAP). She was given low-dose aspirin and was hospitalized and investigated for six days.

On admission, a CT revealed evidence of pulmonary edema. There was no evidence of pulmonary embolus. TTE revealed sinus rhythm and showed a mild degree of global systolic dysfunction (EF 51-53%). There was a possible mild hypokinesis of the anterior interventricular septum. Initial troponin levels were 156, peaked at 195, then fell to 20 two days later.

A persantine myocardial perfusion imaging (MIBI) test showed no evidence of ischemia. CT angiography revealed no coronary artery disease. Myocardial perfusion revealed no scintigraphic evidence for ischemia, but with equivocal left ventricular systolic function. Paroxysmal atrial fibrillation/ flutter was demonstrated, up to 145 bpm with associated palpitations. A 24-hour Holter monitor showed sinus rhythm with multiple episodes of paroxysmal atrial fibrillation (47% of total).

A month later the ECG and TTE were normal. Over the next two months she had episodes of palpitations and atrial fibrillation. This was treated by her cardiologist with sotalol and flecainide, but these were not well tolerated. Three months after the incident she resumed swim training in a pool, but this, like all other exercise, triggered episodes of PAF and was terminated when she felt unwell. Subsequent treatment focused on reducing exercise-induced dysrhythmias.

Comments

Atrial fibrillation is a recognized risk factor for pulmonary edema and may have been the precipitating factor in this patient. However, whether this was PAF-induced IPE, or IPE-induced PAF in a predisposed subject is not known.

CASE 30 (2017)

This 55-year-old man, a very experienced technical diver with more than 8,000 dives, had no cardiorespiratory problems and was physically fit, with a BMI of 28.3 kg/m^2. He conducted a feet-first descent to 48 msw using a CCR with over-the-shoulder counterlungs. He then swam horizontally until some 10-12 minutes into the dive. His old wetsuit was a little tight and needed to be stretched prior to the dive. The water was colder than he was used to, and he had also consumed 500 mL or more of water just prior to diving. There was no aspiration or any exceptional resistance from the CCR. Visibility was good and there was no current. Exertion and stress were minimal.

He developed some difficulty in breathing, with cough and a gurgling sound in his chest. He decided to abort the dive and made an ascent in a vertical head-up position. His symptoms became worse during ascent and he aborted his decompression staging.

On the surface his symptoms worsened, and copious sputum was blood-stained, with a greenish tinge. On board the boat he felt exhausted, but improved rapidly over 20 minutes, although some symptoms persisted, and his chest felt "tight and raw." He was exhausted for several hours. That night he slept in a sitting position. He was back to normal approximately 12-18 hours later.

Medical examination

No investigations were performed at the time, but his general practitioner sent him for cardiac assessment several weeks later. At that time there were no abnormalities detected on ECG or TTE, but his blood pressure was 140/100 mmHg.

He has since conducted another 26 dives in tropical waters, thermally comfortable while wearing a lycra suit, and using his CCR. On one dive, he became slightly short of breath and felt a gurgling in his chest and aborted without further issues. He is now commencing treatment for hypertension and is being investigated for sleep apnea.

Comments

The initial IPE may have been contributed to by cold-water exposure, overhydration and, possibly, a tight wetsuit although none of these triggers were present in the subsequent episode.

CASE 31 (2018)

This 71-year-old male (BMI of 27.1 kg/m^2) had a history of amaurosis fugax and a knee replacement. Two years prior to the incident, a TTE revealed a subaortic valve membrane and minor valvular aortic stenosis. The remainder of the TTE was unremarkable, with normal left ventricular size and function, normal right ventricular size and function and normal pulmonary pressures. He was advised that he could undertake strenuous exercise and was assessed by that doctor as fit to dive. He was taking clopidogrel, rosuvastatin and aspirin. Overall, he had performed more than 1,000 dives over 36 years, without major incident.

On this occasion he made a dive in tropical waters (28°C) to a maximum depth of 20 msw for 42 minutes using nitrox (31%). On descending to about 4 msw, he had trouble with the buoyancy of his camera equipment and surfaced to remedy the problem. This procedure required some exertion, after which he redescended. At 16 msw and after 20 minutes underwater, during which he encountered no current and was not anxious, he developed coughing, which he did into his regulator while he continued the dive. The coughing increased as he ascended from 18 msw and was greatest after surfacing. The cough produced blood-tinged sputum and he was dyspneic. He became more concerned when he became very tired, requiring many rest stops when walking up the steps back to his accommodation. The symptoms began improving soon after he rested but lasted for some hours.

Medical examination

A CXR on admission showed pulmonary edema. The ECG showed sinus bradycardia. Troponin was 120 ng/L around 12 hours post-incident and dropped to 20 ng/L the next day (n = 0-20). D-dimer reduced from 1,090 to 201 ng/mL over the same period (n = 0-600). The TTE indicated mild aortic stenosis, thickened aortic valve and mild aortic regurgitation as well as a reverse EA ratio indicative of impaired diastolic relaxation. He was discharged and advised that he could perform mild diving the next day.

Follow-up testing on return to Australia confirmed exercise-induced LV dysfunction with exercise-induced left BBB. There was no obstructive CAD.

Comments

Several factors in this case may have contributed to the observed pulmonary edema. His past history of subaortic stenosis and valvular changes as well as his diastolic dysfunction and the vasodilator effects of a higher O_2 partial pressure may all have contributed to elevated pulmonary capillary pressures in the setting of increased preload from immersion. While the troponin rise might well have been initially thought to be indicative of an acute myocardial infaction with associated acute pulmonary edema, this was subsequently discounted with a coronary scan.

CONCLUSION

A total of 31 diagnosed IPE incidents in divers were documented. There were two surface snorkelers, 22 scuba air divers and seven nitrox divers that included three closed-circuit rebreathers (CCR). The mean (SD) age was 53 (12) years, 58% of victims were females, and the average dive profile was to a maximum depth of 19 msw for 25 minutes. Six victims (19%) had previous episodes of IPE. There were nine recorded fatalities.

Factors previously identified by others and which may have been contributors were noted. These included: exertion, stress, cold exposure, negative inspiratory pressure, hypertension, overhydration, ascent or surfacing, tight wetsuit, aspiration and certain medications.

Cardiac conditions were frequent and included chronic disorders (valvular pathology, coronary artery disease) and transient disorders (dysrhythmias, transient myocardial dysfunction, takotsubo or stress cardiomyopathy). It is likely that the chronic cardiac disorders may have contributed to the IPE, whereas the transient episodes could be either the sequelae, contributors or coincidental to the IPE.

This series supports the hypothesis that the more elderly IPE subjects are likely to have comorbidities and be susceptible to IPE recurrences and fatalities unless the contributing factors are able to be identified and addressed.

Conflict of interest and funding statements

The authors have declared that no conflict of interest exists with this submission.

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RESEARCH ARTICLE

Immersion pulmonary edema: an analysis of 31 cases from Oceania

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ABSTRACT

Aim: To review incidents of immersion pulmonary edema (IPE) from Oceania, to determine the demographics, diving parameters, and comorbidities that may be related to this disorder.

Method: Incidents of IPE, most of which were documented by Divers Alert Network Asia-Pacific (DAN AP) or reported in our medical literature, were analyzed. They included interviews with the survivors and a review of available medical records. Only incidents diagnosed as IPE by specialist diving physicians or pathologists with experience in the investigation of diving accidents were included.

Results: Thirty-one IPE incidents in divers from Oceania were documented. There were two surface snorkelers, 22 scuba air divers and seven nitrox divers, which included three closed-circuit rebreathers (CCR). The mean (SD) age was 53 (12) years, 58% of victims were females, and the average dive profile was to a maximum depth of 19 msw for 25 minutes. Six victims (19%) had previous episodes of IPE. There were nine recorded fatalities in this cohort.

Medical comorbidities were recorded in 68%, with 42% being cardiac. The latter included valvular disease in 29%, transient cardiomyopathies in 26% and dysrhythmias in 16%.

Conclusion: IPE was more likely in middle-aged females, in experienced divers, and during ascent or after surfacing. Commonly reported associations such as exertion, stress, cold exposure, negative inspiratory pressure, hypertension, overhydration, tight wetsuit, aspiration and certain medications were identified.

This series supports the hypothesis that the elderly IPE subjects are likely to have comorbidities and be susceptible to IPE recurrences and fatalities unless the contributing factors can be identified and addressed.

Pathological and historical perspective

Pulmonary edema is a well-described clinical entity with established causes, recognized symptomatology, standardized investigations and accepted treatments [1]. If it occurs during immersion, then the diagnosis is more problematic, and the etiological factors are more numerous and less validated.

Pulmonary edema develops when fluid accumulates in the lung tissue or alveoli [1]. If the pressure gradient between the pulmonary capillary and the alveolar space exceeds the functional integrity of the capillary/alveolar membrane, fluid accumulates in the alveoli. Thus, a rise in pulmonary capillary pressure, or a reduction in alveolar pressure, or damage to the alveolar-capillary membrane, may contribute, alone or in combination, to pulmonary edema. Also, capillary hydrostatic pressure may exceed the plasma oncotic pressure, favoring transudation of fluid into the alveolus and cause pulmonary edema.

Pulmonary edema in scuba divers (SDPE) was established as a bona fide, if rare, condition when reported in 1981 [2]. It presents clinically with dyspnea, fatigue, cough, frothy expectoration which is often blood-stained, hypoxia and auscultatory signs of pulmonary edema. It is confirmed radiologically by chest X-ray and/or pulmonary CT scan. The clinical symptoms, diagnostic investigations and treatments are not contentious, and so are not analyzed further in this report. Other diving disorders that may contribute to pulmonary edema need to be excluded and are described elsewhere [3].

The early SDPE case series comprised only a handful of otherwise healthy subjects, selected to validate the entity of SDPE and exclude other diagnoses [2-5]. Nevertheless,

KEYWORDS: diving incidents; immersion; pulmonary edema; medical conditions and problems; cardiovascular; deaths

the major initiating factor, the physiological effects of immersion per se, was complicated by two other observed stressors: systemic hypertension and excessive physiological responses to cold exposure [2,4].

Pulmonary edema while swimming was observed, occasionally, in victims who also experienced SDPE. Later it was reported in very fit swimmers, after extreme exertion or overhydration. This latter condition was labeled swimming-induced pulmonary edema (SIPE) and was recorded especially in combat/military swimmers undergoing severe endurance training [6,7]. More pulmonary edema cases were described in triathletes (during their aquatic activities) and even in other species (race horses). There was a presumed relationship between SIPE and the well-described exercise-induced pulmonary edema [8,9].

The entities SDPE and SIPE are collectively termed immersion pulmonary edema (IPE). The demographics of these subgroups differ, as do some of the other contributors and comorbidities.

Subsequently, other series from the Northern Hemisphere included cases with cardiac disorders, either permanent or transitory, associated with SDPE [10-12]. Fatalities from SDPE were reported from the Southern Hemisphere [13].

In a seminal study at Duke University, subjects who had reported symptoms consistent with IPE were monitored and compared to controls who had not [14,15]. They were exposed to immersion, hyperbaria and hyperoxia. Higher pulmonary artery pressures and pulmonary capillary wedge pressures were found in those with IPE, indicating that IPE can be a form of hemodynamic pulmonary edema. It was deduced that cardiopulmonary disease may be a common risk factor in the recreational divers/swimmers (with a mean age of 47.8 ± 11.3 years), whereas pulmonary hypertension may be more relevant in military divers/swimmers (mean age 23.3 ± 6.4 years). They concluded that the role of underlying cardiopulmonary dysfunction may be underestimated, especially in older swimmers and divers, and an episode of IPE should prompt the evaluation of cardiac and pulmonary function.

SDPE had evolved from a presumed disorder of healthy divers into a disease of older divers with multiple comorbidities, especially cardiac [16].

An increasing number of divers have presented with IPE over the last decade, possibly because of the increasing age of divers, a greater recognition of this disorder during that period and a greater use of specific cardiac investigations.

Most of the clinical series described to date are from Europe and North America, with the demographics, diving profiles, possible contributors and comorbidities reflecting the diving population of those regions. Our report is based on cases in Oceania (the Indo-Pacific region), and so complements the previous series. More detailed summaries of the individual cases on which this report is based are available [17].

METHODS

For reporting of fatal cases ethics approval was received from the Victorian Department of Justice Human Research Ethics Committee (to access data from the Australian National Coronial Information System); 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.

Cases included those reported to DAN AP by survivors, instructors and diving physicians from January 2002 to May 2018, inclusive. These were followed up with interviews, where possible, and a review of clinical information and investigations. These victims provided informed, written consent to review and publish their medical and diving data in a non-identifiable form and provided these data for this purpose.

A search was made of the Divers Alert Network Asia-Pacific (DAN AP) internal fatality database and associated autopsies for diving-related deaths in Australia during the same period. In addition, a Medline search was conducted using the terms "diving," "immersion" and "pulmonary edema" to identify cases reported within Oceania. Several of these were followed up with the authors in order to elicit further details.

Only cases validated by a diving physician or pathologist with experience in diving accident investigation were included. The main criteria were: symptomatology being related to immersion, clinical and radiological evidence of pulmonary edema, and/or autopsy findings. Other diving related causes of pulmonary edema were excluded.

We have not itemized the already well-established features of IPE, such as symptomatology and treatment. We have instead documented the features associated with IPE. These may be causative, provoking or contributing factors.

The demographic records were compiled and included age, gender, maximum depth of immersion, dive duration,

Table 1. Demographics of IPE cohort

age (yr)	mean (SD) 53 (12), range 21-67
gender F/M	18/13 (58% female)
maximum dive depth (msw)	mean (SD) 19 (18), range 0-87
incident depth (msw)	mean 14, range 0-70
dive duration (min)	mean (SD) 25 (14), range 4-56
previous episodes of IPE	6/31 (19%)
dive experience* (n = 26)	novice 6/26, moderate 4/26, very 16/26

*novice , <10 dives, moderate 10-50, very > 50

type of diving (snorkel, scuba air, nitrox, rebreathers), depth and time of incident commencement, dive experience and previous IPE incidents. Possible contributing factors, as described previously by others, were also noted when this information was available. These cases often occurred in remote localities, and medical records were sometimes unreliable or incomplete. As a result, the incidences of these possible contributing factors are likely to be underestimates.

The possible aggravating factors, comorbidities and physiological stressors included:

- negative inspiratory pressure (regulator resistance, reduced gas supply, depth, spatial orientation and counterlung positioning);
- chronic cardiac pathology (mitral or aortic valve disease, ischemic heart disease, myocardial fibrosis, ventricular hypertrophy, etc.);
- transient cardiac disorder, (dysrhythmias, stress cardiomyopathies);
- hypertension;
- cold exposure;
- aspiration;
- overhydration;
- drugs;
- ascent or surfacing ;
- anxiety/stress;
- exertion;
- tight wetsuit;
- others.

Clinical summaries of the incidents put these associations and possible contributing factors in context and are available [17].

The subject's decision to continue with an immersion/diving activity after an IPE event was noted in some cases. However, this information was often not available.

The autopsy findings in our cohort were recorded, and the number of cases ending in death was noted. The survivor cohort was derived from victims who received medical attention for IPE and thus was likely an underestimate of the total incidence of IPE.

Some associations, such as medication usage, were recorded but without clinical knowledge of their relevance. Others, such as negative inspiratory pressure, were deduced from the dive data.

The transient cardiomyopathy (stress cardiomyopathy, takotsubo cardiomyopathy and other reversible myocardial disorders such as reversible myocardial dysfunction – SCM/TC/RMD) was assessed based on the clinical data available. As these transient cardiomyopathies are not well defined, an arbitrary checklist was designated, viz: The diver must have a confirmed diagnosis of IPE and have no evidence of coronary artery disease or myocardial ischemia on conventional cardiac investigation or autopsy. With this prerequisite, three of the following five characteristics were required:

- transient ST-T changes on the ECG, from the time of the incident;
- transient elevation of cardiac enzymes (especially troponins) from the time of the incident;
- ventricular wall motion dysfunction;
- excessive stress events;
- typical myocardial histopathology at autopsy.

RESULTS

Details of 31 cases of IPE from Oceania, from January 2002 to May 2018, inclusive, were documented [17]. There were two surface snorkelers, 22 scuba air divers and seven nitrox divers, which included three closed-circuit rebreathers (CCR). The relevant demographics are shown in Table 1.

Death, with autopsy findings, coroners' inquests and boards of inquiry, occurred in 9/31 cases. Cardiac anomalies were substantial but diverse in 13/31 cases. These included:

- mitral or aortic valve disease of greater than mild severity in 9/31;
- transitory cardiomyopathies (SCM/TC/RMD) in 8/31 cases;
- ventricular wall dyskinesis in 6/31;
- a significant rise in serum troponin level was recorded in 8/10, a slight rise of 4x normal in one and no rise in another. In none of these cases was there other evidence of myocardial ischemia or infarction'
- dysrhythmia clinical history (other than ventricular premature beats) in 5/31;
- autopsy findings included left ventricular hypertrophy (5/9), mitral or aortic valve disease (4/9), myocardial fibrosis (3/9) and contraction bands (3/9).

Left heart impairment, exacerbated by situational factors, was the presumed contributor to IPE in most of these cases. Detailed and more specific cardiac information is available elsewhere [17].

Hypertension was present in 7/31 cases. Excessive exertion was specifically noted in the clinical history in 12/31 cases, and anxiety/stress in 11/31.

It is possible that drugs may have contributed to between 6-10/31 incidents, mainly beta blockers [18], but also sympathomimetics, arrhythmogenics, diclofenac and once with possible edema-inducing pregabalin.

Excess negative inspiratory pressure was likely in 3/31 of cases, based on subjective assessments. This was implied from the divers' impressions, regulator resistance, and a low-on-air situation, postural effects with surfacing and CCR dynamics.

A tight wetsuit or buoyancy compensation device was noted in 6/31 cases.

Possible slight aspiration or swallowing of seawater was elicited on specific interrogation on three occasions. This was an admitted possibility, more than an observation, and was not followed by the typical salt water aspiration syndrome [3]. One case specified swallowing sea water. In the one definite case of aspiration, this occurred on a previous dive a day earlier than the incident and without clinical symptoms supervening

Only 5/31 incidents were in cold water (15°C or lower), and even then, there was appropriate insulation worn and rarely an excessive cold sensation described. At least 10/31 were in waters > 20°C; full temperature range was -1°C to 30°C.

Voluntary over-hydration was possible in 4/31.

The maximum dive depth averaged 19 msw. Symptoms commenced at an average depth of 14 msw after an average of 24 minutes diving, and worsening upon ascent and surfacing.

Some individual cases had very specific possible but contentious contributing factors, such as asthma, diabetes, an adrenal adenoma, a dopamine-secreting non-malignant vagus paraganglioma, and gas toxicity.

Only 7/31 incidents could be classified as idiopathic IPE, and some of these may well have been so designated because of inadequate or delayed interrogation and investigation. Possible contributors to the IPE incidents are shown in Table 2.

DISCUSSION

IPE Demographics

Explanations for most of the possible contributing factors are postulated elsewhere [1-5,8,18,19].

In the Oceania case series, the clinical symptoms of IPE replicated those of other series [2,4,5,10,11,12,19]. In most of the larger Northern Hemisphere IPE case series, females dominated, as did older divers, and they were diving in cold water (< 15°C) to an average depth of 37 msw [5]. The earlier series excluded those with cardiac comorbidities.

The demographic factors in this Oceania IPE series are consistent with the various North Hemisphere series in that they were older than the average scuba diver, with females predominating – reversing the gender ratio of the diving population [20]. Most were experienced divers. There was also a high incidence of recurrences.

The diving circumstances of the Oceania cohort did differ in some respects from the Northern series. Our cases were in warmer waters, with shallower shorter dives and less decompression stress. They had an overwhelming predominance of cardiac co-morbidity and a higher fatality rate.

Immersion

The one common feature in this disorder is the exposure to immersion. This causes a central blood shift, which increases pulmonary capillary pressure and the cardiac preload. Immersion with cold exposure increases vasoconstriction and systemic hypertension, with an increased afterload on the left heart [8,18,19,21]. These two factors together create an increased pulmonary capillary/alveolar gradient favorable to the development of pulmonary edema. Engorgement of the pulmonary vessels may contribute to capillary stress failure [1].

Table 2. Associations and possible contributors to IPE

	frequency	%
ascent or surfacing	21/29	72
medical comorbidity	21/31	68
cardiac comorbidity	13/31	42
mitral/aortic valve dysfunction	9/31	29
transient cardiomyopathy	8/31	26
dysrhythmia	5/31	16
exertion	12/31	39
anxiety/stress	11/31	35
drugs	6-10/31	26
hypertension	7/31	23
tight wetsuit/BCD	6/31	19
cold water exposure	5/31	16
aspiration/swallow water	5/31	16
overhydration	4/31	13
negative inspiratory pressure	3/31	10
nil identified other than immersion	7/31	23

Immersion and the many physiological implications of diving may trigger the development of IPE. This and previous studies attempt to recognize these aggravating factors.

Without any evident contributing factors, other than immersion effects, IPE could be classified as idiopathic. If there are evident provoking or contributing factors, other than immersion, IPE could be described as symptomatic, to be qualified by the contributing factors.

Comorbidity

Previously reported subgroups of Australian divers have had 28-34% medical comorbidities with only 2-3% being cardiac [20]. However, the prevalence of comorbidities in the non-IPE Australian diver groups is likely to be underestimated, as they were not subjected to the same degree of medical examination as this Oceania IPE series.

In the Oceania IPE series, medical comorbidity was present in 68% (mean age 53 ± 12 yr) of the divers, with 62% of these being cardiac. In a Duke University study, 36 IPE subjects were identified (mean age 50.11 ± 10.8 years), of whom 72.2% had one or more significant medical comorbidities [14].

Ascent and surfacing

Ascent to the surface and exiting the water is required once IPE has developed [3]. However, aggravation of IPE on ascent and after surfacing was encountered in both the Oceania and Northern Hemisphere series [5,19,22, 23]. This accentuation of IPE could be explained by:

- spatial positioning effects on negative static lung loads, whenever the diver is ascending vertically or in the head-out position on the surface;
- reduction of respiratory oxygen pressures during ascent;
- redistribution of pulmonary edema fluid from the expansion of intrathoracic gas, due to Boyle's law;
- The natural progression of the disease with time.

Cardiac disorder

Chronic cardiac pathology is recognized as a cause of left ventricular failure and may be a basis on which IPE develops. The pathologies include cardiac ischemia, coronary artery disease and structural disease, especially with mitral and aortic valve dysfunction.

Transient cardiac disorders are also associated with IPE, either as contributors or sequelae. These include dysrhythmias and transient cardiomyopathies.

A recent review highlighted the increasing association of IPE with cardiac dysfunction and deaths [16]. This and multiple case reports also demonstrated an association of IPE and takotsubo cardiomyopathy [22,23,24]. Transient cardiomyopathies encompass such clinical subdivisions as SCM, TC, "atypical TC" and RMD, depending on which characteristic appears more prominant [25]. Coronary artery disease needs to be excluded for these diagnoses. In one series of 54 divers with SDPE, 28% were found to have RMD, including takotsubo. Most had elevated cardiac troponin levels, electrocardiograhic and/or echocardiographic abnormalities [26]. These disorders could be either a consequence of IPE or a contributor to it.

Takotsubo cardiomyopathy was first described in 1990. It is a clinical syndrome that occurs in the absence of significant coronary artery pathology, but presents as an acute, reversible disorder of the heart, with dyspnea or pain. It may be related to a catecholamine release causing a "stunning" of the myocardium. A stressful physical or emotional trigger is often, but not always, present. Women are affected in 90% of incidents, recurrences are common and there is a fatality rate of about 5% for those hospitalized. There is a transient left ventricular wall dyskinesis, often presenting as a ballooning and usually demonstrated by TTE. ECG abnormalities are often suggestive of ischemia. There is a modest elevation of cardiac enzymes and troponins [25]. Because it is transient, delay in investigation can result in a failure to diagnose this disorder.

The incidence of transient cardiac abnormalities is almost certainly an underestimate, as during the chronological first half of this series, cardiac investigations were less frequent and less extensive. During that period the association of IPE and transient cardiac disease was only just being recognized. Thus, for example, cardiac troponin levels were performed in only 3/10 in the earlier half of the series.

Autopsy findings of SCM/TC vary from insignificant cardiac histology to focal necrotic lesions, inflammatory changes, interstitial fibrosis and contraction bands (myocytolysis) – especially in the left ventricle and possibly dependent on the survival time.

Exertion

During strenuous exercise, the lung must accommodate a more than doubling of the pulmonary vascular flow [1]. Elevated pulmonary artery and left atrial pressure, coupled with a decreased intrathoracic pressure during inspiration, results in increased capillary transmural pressures and the exudation of fluid from the capillary to the alveolus.

Anxiety/stress

Anxiety is a contributing factor to many of the IPE scenarios. It is associated with hypertension, increased respiration, cardiac disorders such as ischemia, dysrhythmias and SCM/TMD/TC.

Equipment constriction

This may contribute to increased work of breathing, centralization of blood volume, and anxiety. However, any relationship between IPE and a tight wetsuit or buoyancy compensator remains conjectural.

Drugs

Drugs may influence the likelihood of IPE. Negative inotropes, including beta blockers, weaken muscular contraction and have various cardiorespiratory effects. Sympathomimetics may potentiate hypertension, dysrhythmias or SCM/TC/TMD. The contribution of drugs was conjectural and could not be quantified in this report.

Hypertension

Although systemic hypertension may play a role in increasing the afterload on the left heart, and despite its association with the other cardiac stressors (e.g., cold exposure, anxiety and exertion), this was not as frequent as anticipated. Nevertheless, its incidence was greater than recently reported in some other Australian diver cohorts, including divers of a similar age [20].

Minor aspiration/swallowing of seawater

The occurrence of subclinical minor aspiration or swallowing of seawater in the Oceania series did not replicate the drowning syndromes or the saltwater aspiration syndrome, as described [3]. It may still have contributed to IPE by damaging the integrity of the pulmonary alveolar-capillary barrier, if seawater was inhaled directly, through a snorkel, or sprayed from a leaking regulator.

Negative-pressure inspiration

Negative respiratory pressure may occur under certain circumstances. This reduces intra-alveolar pressures, increasing the capillary-to-alveolar gradient and may enhance pulmonary capillary engorgement. Negative respiratory pressure may occur from a poorly tuned regulator, with increased resistance to breathing, increased gas density with depth, and increased respiratory volumes with exertion or anxiety. With CCRs, the added respiratory resistances of the equipment, the relative position of the counterlung and the spatial orientation of the diver may influence the extent of the negative inspiratory pressure.

Cold

Exposure to cold may intensify systemic hypertension and thus increase afterload on the left heart, but thermal stress was not particularly frequent in this series. Most incidents occurred in temperate or tropical waters and with adequate thermal protection. Thermal protection does not preclude the cooling effect of the gas laws, however. As respiratory gases are decompressed prior to inhalation the temperature of the gas decreases. This is inevitable with use of open-circuit scuba. Cold could potentially increase cardiac preload, enhancing redistribution of blood volume to the central circulation.

Voluntary overhydration

This was not common and not excessive in this series, as it was in others. The rationale for its use was to reduce decompression sickness.

Oxygen

Although there is no disagreement regarding the value of oxygen supplementation in treatment of IPE, there is no such consensus regarding its preventative effect. Seven of our cases were classified as technical divers employing a higher partial pressure of oxygen (PPO_2) near the end of the dive in which they developed IPE.

Recurrences

As IPE is purportedly a rare event, recurrences imply a predisposition. This recurrence may be based on individual susceptibilities, possibly from one of the medical comorbidity disorders, or contributory diving and environmental conditions that are then replicated to produce a recurrence.

The current experience with IPE, especially related to recurrences, cardiac implications and fatalities, has imposed a more conservative approach to resumption of scuba diving or snorkeling. This is discussed elsewhere [3,16].

LIMITATIONS

As with most other clinical series of IPE, it is likely that there is a selection bias by recording the more severe and fatal events, because these are the ones likely to be investigated or be reported.

Many cases of IPE, even some relatively severe cases, rapidly improve after retrieval from the water and thereby avoid medical intervention. Some IPE events are misdiagnosed as an aspiration/drowning incident and other cases are only reported in the internet blogospheres. Thus, it is reasonable to assume that IPE is often undiagnosed, and its frequency underestimated.

There is particular difficulty in differentiating between IPE and drowning at autopsy and cases of IPE may be attributed to drowning [3,27,28].

The associations of some transient factors could in some cases be the result of IPE rather than its causation.

It was not possible to incriminate or quantify certain possible contributors. These include: cold-water exposure (as there were far more cases in temperate and tropical waters), the influence of drugs, and the relative influence of negative inspiratory pressures (as these were unrecorded and thus a matter of clinical conjecture).

CONCLUSION

In this series of 31 IPE incidents from Oceania, cardiac disorders dominated the co-morbidities. These included mitral or aortic valve disease, stress cardiomyopathy, takotsubo or reversible myocardial disorder and dysrhythmias.

Coronary artery disease, dysrhythmias and structural cardiac pathology should be investigated and excluded in possible IPE cases.

Prior to 2000 there were few cases of SCM/TC/RMD or other takotsubo-type cardiomyopathies being reported, and none with IPE. As over a quarter of our cases were identified as having a transient cardiomyopathy, it is likely that this association with IPE is not coincidental. All cases of IPE should include an early chest X-ray or CT scan, ECG, TTE and cardiac biological markers, including cardiac troponins. If abnormal, these tests should be repeated.

Other suggested contributing factors such as exertion, cold exposure, negative inspiratory pressure, hypertension, overhydration, tight wetsuit, aspiration and certain medications were also identified in various cases.

This series supports the hypothesis that the elderly IPE subjects, mostly females, are likely to have comorbidities and be susceptible to recurrences and fatalities, unless the contributing factors can be identified and addressed.

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RESEARCH ARTICLE

Risk factors for immersion pulmonary edema in recreational scuba divers: a case-control study

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ABSTRACT

Background: Immersion can cause immersion pulmonary edema (IPE) in previously healthy subjects. We performed a case-control study to better identify IPE risk factors.

Methods: We prospectively included recreational scuba divers who had presented signs of IPE and control divers who were randomly chosen among diving members of the French Underwater Federation. We sent an anonymous questionnaire to each diver, with questions on individual characteristics, as well as the conditions of the most recent dive (controls) or the dive during which IPE occurred. Univariate logistic regressions were performed for each relevant factor. Then, multivariate logistic regression was performed.

Results: Of the 882 questionnaires sent, 480 (54%) were returned from 88 cases (90%) and 392 control divers (50%). Multivariate analysis identified the following independent risk factors associated with IPE:

- being aged over 50 years ((OR) 3.30, (95%CI) 1.76-6.19);
- female sex (OR 2.20, 95%CI 1.19-4.08);
- non-steroidal anti-inflammatory drug (NSAID) intake before diving (OR 24.32, 95%CI 2.86-206.91);
- depth of dive over 20 m (OR 2.00, 95%CI 1.07-3.74);
- physical exertion prior to or during the dive (OR 5.51, 95%CI 2.69-11.28);
- training dive type (OR 5.34, 95%CI 2.62-10.86); and
- daily medication intake (OR 2.79, 95%CI 1.50-5.21); this latter factor appeared to be associated with hypertension in the univariate analysis.

Conclusions: To reduce the risk of experiencing IPE, divers over 50 years of age or with hypertension, especially women, should avoid extensive physical effort, psychological stress, deep dives and NSAID intake before diving.

KEYWORDS: pulmonary edema; scuba diving; immersion

INTRODUCTION

Several studies have reported that immersion can cause stress failure of the blood-gas barrier leading to immersion pulmonary edema (IPE) in previously healthy subjects during endurance swimming, breath-hold diving and scuba diving [1-8].

The pathophysiology of IPE is not completely understood and appears to be multifactorial. In all cases, the main issue is the redistribution of peripheral blood into central circulation due to immersion, which leads to an increase in cardiac preload as well as in pulmonary vascular pressure and a decrease in pulmonary compliance. Emotional stress and physical exertion contribute to this high vascular pressure, which may be further increased by wearing a diving wetsuit [9]. Cold exposure causes arteriolar constriction that may increase cardiac afterload; the wetsuit can also impair ventilatory mechanics [10]. During scuba diving, subjects undergo other respiratory constraints such as increased inspired gas density and resistance due to the breathing apparatus, leading to an increase in the respiratory workload [11].

IPE is thought to involve two populations: relatively young subjects such as triathletes or military divers under intense physical exertion during immersion and older recreational divers with prior cardiovascular abnormalities and probably undiagnosed left ventricular dysfunction [12].

The purpose of the present study was to analyze the risk factors of IPE during recreational scuba diving with a case-control study.

METHODS

Case and control subjects and study design

From March 2011 to November 2015, we prospectively recruited recreational scuba divers who presented signs of IPE as defined in Table 1. The majority of these divers were treated in two French hyperbaric centers: Brest, near the Atlantic Ocean and Toulon, near the Mediterranean Sea.

For each case, we contacted eight control divers randomly chosen from diving members of the French Underwater Federation (FFESSM). We excluded subjects under 18 years old, subjects who had a contraindication for diving exceeding one month at the time of the survey and subjects with a history of respiratory illness while diving.

We sent by post the same questionnaire to all divers, cases and controls, with questions on individual characteristics (age, sex, weight, size, smoking status, cardio-respiratory and metabolic history, daily medication), as well as the conditions of the most recent dive (controls) or of the dive during which IPE occurred (cases) and health status at the moment of the dive (sickness at the moment of the dive, medication taken before diving). When responders answered "yes" to the questions on medication intake, they were asked to name the medication.

The responses to the questionnaires were collected anonymously.

The survey protocol was approved by our institutional Ethics Committee (Comité d'éthique du CHRU de Brest) and the French National Data Protection Authority (CNIL).

Data analysis

Divers' characteristics were expressed as mean and standard deviation for continuous variables and as number and percentage for categorical variables. Student's t-test was used to compare means between the two diver groups (case group and control group). A non-parametric Mann-Whitney test was used when the distribution was not normal. Chi-square test (or an exact Fisher test when appropriate) was used to compare proportions. Univariate logistic regressions were performed for each relevant factor. Then, multivariate logistic regression was performed using a backward selection procedure with a significance level of 0.05. The statistical analysis was performed using SAS software, version 9.4.

Table 1: Inclusion and exclusion criteria for cases

CASE INCLUSION CRITERIA	
	onset of signs during immersion
and	
	respiratory sickness with dyspnea
and/or	***cough***
and/or	***hemoptysis*** and/or ***frothy or bloody sputum***
and/or	***weakness***
and	***chest X-ray or CT scan confirming the diagnosis***
CASE EXCLUSION CRITERIA	
	water aspiration
or	***rapid ascent with respiratory blockage***
or	***signs of pneumothorax or pneumomediastinum***

RESULTS

In total, 882 questionnaires were sent to 98 cases and 784 control divers. Of these, 480 (54%) were returned, with 88 from IPE cases (90%) and 392 from control divers (50%), thus allowing reliable analysis of data (i.e., 4.4 control cases for every IPE case).

The sex distribution between responders and non-responders was not statistically different: 69.4% (279) men in the non-responder group versus 67.5% (324) in the responder group ($p = 0.514$). The mean age of responders was significantly higher than that of the non-responders (46.6 years ± 11.9 years versus 42.5 ± 12.7, $p < 0.001$).

Individual characteristics are presented in Table 2. Case divers were significantly older. The proportion of women was significantly higher in the case group, as was history of arterial hypertension, daily medication intake and hypotensive drugs intake. No statistical difference was found for the intake of other drugs.

Dive conditions and health status at the time of the dive (dive during which IPE occurred for the case divers or most recent dive for the control divers) are presented in Table 3. The mean depth of the cases' dives was significantly greater than that of the controls and the mean duration of the cases' dives was significantly shorter than that of the controls. The cases' dives were predominantly associated with training dive sessions and exertion prior to or during the dive.

Univariate analysis and the multivariate analysis are presented in Table 4 and show that the independent risk factors associated with IPE were being older than 50 years of age (odds-ratio (OR) 3.30, 95% confidence interval (95%CI) 1.76-6.19), female sex (OR 2.20, 95%CI 1.19-4.08),

Table 2: Individual characteristics of control divers and case divers

Variable		Cases (N=88)	Controls (N=392)	p*
	N	88	392	
Mean age (yr)		50.9 (SD10.62)	45.3 (SD11.87)	<0.001
Age (two age classes)	< 50 yr	33 (37.5%)	246 (62.8%)	<0.001
	≥ 50 yr	55 (62.5%)	146 (37.2%)	
Sex	Male	47 (53.4%)	277 (70.7%)	0.002
	Female	41 (46.6%)	115 (29.3%)	
Body Mass Index: N		88	385	0.033
	mean	25.9 (SD 4.18)	25.0 (SD3.67)	
Obesity: yes		13 (14.8%)	35 (8.9%)	0.119
	missing data	0 (0%)	7 (1.8%)	
Cigarette smoker: yes		9 (10.2%)	66 (16.8%)	0.121
	missing data	0 (0%)	1 (0.3%)	
New dive after long hiatus: yes		18 (20.5%)	82 (20.9%)	1.000
	missing data	1 (1.1%)	4 (1%)	
Total number of dives in lifetime	1-50	20 (22.7%)	100 (25.5%)	0.692
	51-200	32 (36.4%)	127 (32.4%)	
	>200	33 (37.5%)	160 (40.8%)	
Hypertension		19 (21.6%)	26 (6.6%)	<0.001
History of cardiomyopathy		4 (4.5%)	9 (2.3%)	0.270
Hyperlipidemia		16 (18.2%)	44 (11.2%)	0.075
Daily medication intake		43 (48.9%)	84 (21.4%)	<0.001
Daily hypotensive medication intake		17 (19.3%)	26 (6.6%)	<0.001
Daily diabetes medication intake		4 (4.5%)	4 (1%)	0.041
Daily antiplatelet medication intake		2 (2.3%)	4 (1%)	0.304

Data are presented as mean and standard deviation (SD) for continuous variables and as number and percentage for categorical variables.

* p-value from chi-square or Fisher test for proportions or from Student's t-test or Mann-Whitney test for means

non-steroidal anti-inflammatory drugs (NSAID) intake before diving (OR 24.32, 95%CI 2.86 – 206.91), depth of dive greater than 20 m (OR 2.00, 95%CI 1.07 – 3.74), physical exertion prior to or during diving (OR 5.51, 95%CI 2.69 – 11.28), training dive type (OR 5.34, 95%CI 2.62 – 10.86) and daily medication intake (OR 2.79, 95%CI 1.50-5.21).

DISCUSSION

Our study explored the frequently alleged reported risk factors, such as age, physical exertion and daily medication intake (primarily for hypertension). In addition to these factors we also found a risk associated with being female, dive depth, training dives and NSAID intake before diving. To our knowledge, this is the first study on the risk factors of IPE using a case-control study design with a control group randomly chosen from a large population of scuba divers.

Table 3: Dive conditions and health status at the time of dive

Variable		Cases (N=88)	Controls (N=392)	p*
Feeling ill before diving		4 (4.5%)	15 (3.8%)	0.761
	missing data	1 (1.1%)	1 (0.3%)	
Medication intake before diving (other than daily medication)		23 (26.1%)	35 (8.9%)	<0.001
	missing data	0 (0%)	1 (0.3%)	
NSAID intake before diving		12 (13.6%)	1 (0.3%)	<0.001
Seasickness medication intake before diving		3 (3.4%)	7 (1.8%)	0.401
Antibiotic intake before diving		0 (0%)	2 (0.5%)	1.000
Nasal congestion medication intake before diving		0 (0%)	3 (0.8%)	1.000
Mean dive depth (msw)		29.7 (SD 12.18)	26.1 (SD10.91)	0.006
	N :	87	381	
Dive depth				0.034
	<= 20 m	28 (31.8%)	170 (43.4%)	
	> 20 m	59 (67%)	211 (53.8%)	
Mean dive duration (min)		25.9 (SD 11.00)	43.9 (SD13.32)	<0.001
	N	82	373	
Type of breathing gas				0.054
	Air	80 (90.9%)	352 (89.8%)	
	Nitrox	4 (4.5%)	35 (8.9%)	
	Trimix	2 (2.3%)	1 (0.3%)	
Type of dive				<0.001
	Training dive	36 (40.9%)	40 (10.2%)	
	Exploratory dive	49 (55.7%)	340 (86.7%)	
Feeling cold		20 (22.7%)	60 (15.3%)	0.088
	missing data	1 (1.1%)	3 (0.8%)	
Thermal protection suited to the water temperature				0.092
	No	11 (12.5%)	26 (6.6%)	
	Borderline	6 (6.8%)	32 (8.2%)	
	Yes	58 (65.9%)	312 (79.6%)	
Physical exertion before and/or during diving		34 (38.6%)	32 (8.2%)	<0.001
	missing data	1 (1.1%)	7 (1.8%)	

Data are presented as mean and standard deviation (SD) for continuous variables and as number and percentage for categorical variables.

* p-value from chi-square or Fisher test for proportions or from Student's t-test or Mann-Whitney test for means; NSAID : Non-steroidal anti-inflammatory drug

Table 4: Univariate and multivariate analyses

Variable	Univariate analysis OR (95% CI)	p*	Multivariate analysis OR (95% CI)	p†
Age ≥ 50 yr	2.81 (1.74-4.53)	<0.001	3.30 (1.76-6.19)	<0.001
Female	2.10 (1.31-3.37)	0.002	2.20 (1.19-4.08)	0.012
Daily medication intake	3.50 (2.16-5.68)	<0.001	2.79 (1.50-5.21)	0.001
NSAID intake before diving	61.74 (7.91-481.83)	<0.001	24.32 (2.86-206.91)	0.003
Dive depth > 20 m	1.70 (1.04-2.78)	0.035	2.00 (1.07-3.74)	0.031
Physical exertion before and/or during diving	7.08 (4.03-12.42)	<0.001	5.51 (2.69-11.28)	<0.001
Training dive	6.24 (3.64-10.72)	<0.001	5.34 (2.62-10.86)	<0.001
Hypertension	3.88 (2.03-7.39)	<0.001		
Hyperlipidemia	1.76 (0.94-3.29)	0.077		
Medication intake before diving	3.60 (2.00-6.48)	<0.001		
Feeling cold	1.64 (0.93-2.89)	0.090		
Obesity	1.73 (0.87-3.43)	0.115		
Cigarette smoker	0.56 (0.27-1.17)	0.125		
Thermal protection suited to the water temperature				
Borderline vs No	0.44 (0.14-1.36)	0.102		
Yes vs No	0.44 (0.21-0.94)			

* p-value from Chi-square or Fisher test for proportions or from Student's t-test or Mann-Whitney test for means; † p-value from Wald test; OR odds ratio; 95% CI, 95% confidence interval; NSAID: non-steroidal anti-inflammatory drug

Subclinical pulmonary edema may be quite common after an open-sea scuba dive. One report showed that a scuba dive can lead to increased right-sided cardiac preload and higher pulmonary arterial pressures without increase in left ventricular stroke volume in a young population of professional divers [13]. An imbalance between right and left ventricular stroke volumes causes an accumulation of fluid in the pulmonary vasculature [14]. Fluid clearance by the lymphatic system is increased by hyperventilation during exercise [15]. At maximum work in prone swimming, minute ventilation and breathing rate seem to be lower compared to maximum work on land [16]. Poor coordination between breathing and swimming stroke may hamper the ability to increase minute ventilation and may limit the ability to increase fluid clearance [17]. Acute pulmonary edema occurs when hydrostatic pulmonary capillary pressure is high and when the lymphatic system becomes overloaded. Small modifications that increase this imbalance between the right and left ventricles can lead to symptomatic pulmonary edema.

Age is a commonly suggested risk factor in the majority of IPE cases reported from recreational practice. Peacher, et al. report a mean age of 40-49 years in IPE cases involving recreational divers [12], and several case reports confirm that IPE occurs mostly in divers older than 40 years [18]. Our case-control study demonstrated that IPE divers were significantly older than controls. Cardiorespiratory changes associated with aging tend to increase inspiratory workload, particularly upon exertion [19,20], and cause progressive alteration of myocardial contractility [21]. Mean pulmonary arterial pressure (MPAP) during exercise is also age-related, with values that can

exceed 30 mm Hg during mild exercise, particularly in elderly individuals [22]. Daily medication intake appeared to be another independent risk factor in the multivariate analysis: It may be related to hypertension, as there was a significant difference between cases and controls for a history of hypertension and hypotensive medication intake in the comparison of cases and controls and in the univariate analysis. Interestingly, hypertension is another common risk factor suggested in case reports [12,23] and could be a risk factor associated with a recurrence of IPE [24]. Greater systemic vascular resistance combined with reduced myocardial deformation capacity due to left ventricular hypertrophy predisposes to an inability to increase left ventricular stroke volume appropriately, which may in turn accentuate the ventricular stroke volume imbalance [14]. Furthermore, not surprisingly, physical exertion was revealed as another risk factor. IPE cases have been described during the swim leg in triathletes [8] or in military divers [3]. During exercise MPAP increases as does the cardiac output. This increase is proportional to the workload and more pronounced in immersion with high interindividual variability that may explain individual susceptibility [25]. In a case-control study, Moon, et al. found an exaggerated increase in MPAP and pulmonary artery wedge pressure (PAWP) during exercise in individuals who have experienced IPE that could be reduced by the administration of sildenafil prior to the exercise in immersion [26].

Although men can be afflicted with IPE, several case reports have pointed out that the proportion of women with IPE seems to be higher than the proportion of women in the diver community [7]. Our study confirmed this sex difference. Women have smaller lung volumes and airway diameters, leading to the development of higher mechanical ventilatory constraints and of more intensive utilization of their ventilatory reserve compared with men during exercise [27]. Interestingly, women are more prone to developing hypoxemia even at submaximal exercise intensity. This may be due in part to their increased mechanical ventilatory constraints [28]. Greater alveolar pressure variations may weaken the blood-gas barrier and make women more prone to stress failure of this barrier. Reversible cardiomyopathy may be associated with IPE and may result from catecholamine release during psychological stress and from tissue hypoxia related to IPE, but no sex difference has been explicitly demonstrated [29], although there is a strong association between menopausal women and stress cardiomyopathy such as the takotsubo syndrome [30].

The influence of the dive depth can be attributed to several factors. When symptoms occur at great depth, ascension may require more time and thereby lead to a more serious injury likely to be more easily diagnosed than a mild injury. Depth may be associated with psychological stress, cold exposure, hyperoxia, high breathing workload, with an increase in inspired gas pressure and decompression stress. Hyperoxia increases systemic vascular resistance [31]. However, it may have a relatively protective effect on pulmonary vascular pressure at thermoneutrality, or have no effect at all, which is not consistent with hyperoxia as a risk factor for IPE [32].

We attempted to evaluate the role of psychological stress by asking questions about the personal perception of the diving experience, whether the dive had occurred after a long hiatus, or on the number of dives performed during last year, but there were no differences between the groups. However, training dives was revealed as an independent risk factor, possibly associating psychological stress and exertion.

NSAID intake before diving has been suggested as a risk factor in a case of pulmonary edema [33]; in a retrospective survey, Miller found fish oil consumption as an independent risk factor in triathletes [8]. The importance of NSAIDs may be attenuated in our study by the fact that only a few divers in this study admitted taking this type of medication before diving. Nevertheless, these divers were mostly in the case group. NSAID intake may increase the risk of IPE because it slightly increases systemic blood pressure; it may also damage pulmonary capillary integrity [33].

We failed to show any influence of cold exposure. The subjective perception of cold was not different between cases and controls. Furthermore, our assessment of whether the thermal protection (diving suit) was suitable, unsuitable or borderline with respect to temperature and to dive duration showed no difference between the two groups. The lack of a cold effect was unexpected because cold is frequently suspected to be risk factor [1,18]. This discrepancy may be due to the limited range of water temperatures recorded in this study involving divers mostly from metropolitan France.

LIMITATION

The main limitation of this study includes self-reported risk factors. Self-reported health status – in particular, silent diseases such as hypertension, diabetes or mild cardiovascular abnormalities – may be underestimated in the population, especially for the control divers who

probably did not undergo medical examination as thoroughly as case divers. Diving conditions may not be reliably reported because divers filled out the questionnaire retrospectively. We tried to ask only for objective data because subjective feelings during a dive, such as psychological stress, are more likely to be distorted when retrospectively reported.

Only 54% of the divers who received our questionnaire answered, with a greater participation rate in case divers than control divers. This difference in participation rate can also contribute to a risk factor selection bias. The lack of response risk was taken in account when elaborating the study design. Miller, et al. obtained responses from about one-third of the people who actually received the newsletter he used to contact the triathletes [8]. Pons, et al. obtained 460 responses from 1,250 divers contacted (36.8%) [34]. We contacted eight control divers for each case to obtain three responses: We obtained 4.4 control responses for each case, which was more than expected.

We analyzed whether there was a sex or age difference between responders and non-responders and found only an age difference, thereby enhancing the significance of the age risk factor.

The incidence of clinical IPE is not well known. In a survey of 460 active scuba divers, 1.1% had a history consistent with the development of IPE [34]. A survey carried out by the French Ministry of Sports estimated the population of scuba divers to be about 340,000 [35]; if 1% of this population were to experience IPE, there should be 3,400 injured divers in France, which is not reflected in the small size of our case group and the small number of case reports published. This injury may be under-recognized and underdiagnosed. Furthermore, there is a risk of recurrence, reportedly reaching up to 30% of cases [36]. IPE is a cause of death that is probably under-reported [37]. A better understanding of the mechanism and risk factors is absolutely necessary to improve prevention.

CONCLUSION

Based on our analysis, we recommend that divers older than 50 or with hypertension, especially women, avoid strenuous effort, psychological stress and deep dives. In particular, diving to great depths – e.g., deeper than 20 meters – appears to increase the risk of IPE occurrence, and further complicates the management of respiratory distress in case of IPE by increasing the time to exit the water and adding a risk of decompression illness. Finally, NSAID intake before diving appears to be associated with an increased risk of IPE. This may require further studies to better analyze its role and the mechanisms involved.

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Conflict of interest

The authors report no conflict of interest with the submission of this paper.

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CLINICAL COMMUNICATION

Proposal of a new scoring system for equalization problems during freediving

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ABSTRACT

Objective: Scuba diving and freediving are popular activities around the world, and their growth has increased the frequency of related pathology. A good ability to equalize is of paramount importance for diving. This is especially true for freediving, during which dive time is limited to just one breath. Even though equalization disorders are quite common in divers, a scoring system does not exist to date. In this paper we propose a new scoring system for equalization problems of freedivers: the EP score – shorthand for "equalization problems."

Methods: We administered the EP score assessment to 40 Italian freediving spearfishermen who were divided in two groups: Group A comprised 20 freedivers complaining of equalization problems and multiple barotraumas but totally asymptomatic in their everyday lives. These individuals had already received medical treatment and nasal surgery without improvement and then had undergone Eustachian tube balloon dilation. Group B comprised 20 healthy freedivers without any history of equalization disorders.
We performed a statistical analysis to evaluate the reliability of this scoring system and to evaluate its usefulness in diagnosis and follow-up.

Results: Our data show substantial statistical differences between healthy freedivers and freedivers complaining of equalization disorders (Z-Score = -5.396 at $p < 0.05$); data do not show any statistical difference between healthy freedivers and patients successfully treated by Eustachian tube balloon dilation (U-value = 152.5 and Z-Score= -1.271 at $p < 0.05$).

Conclusion: The EP score assessment seems to be a reliable tool to quantify equalization disorders during freediving and to evaluate how the difficulty varies over time and after treatment. Since equalization disorders could be present in different populations, the EP score assessment could be applicable to a wider group.

KEYWORDS: score; ear barotrauma; Eustachian tube; equalization; diving; freediving

INTRODUCTION

Middle ear pressure regulation is a complex mechanism controlled primarily by the Eustachian tube [1-3], a structure connecting the middle ear to the nasopharynx. It is approximately 44 mm in length and includes a medial cartilaginous portion (two-thirds) and a lateral bony part (one-third) [4]. At rest the cartilaginous portion of the tube is collapsed; it opens for about 0.4 seconds 1.4 times each minute during swallowing [5]. This is thanks to the paratubal muscles, primarily the tensor veli palatini and secondary levator veli palatini [6,7].

When a rapid change in atmospheric pressure occurs – such as during scuba diving, freediving, flying, hyperbaric chamber therapies – Eustachian tube equalization capability is very important to avoid injuries to the middle or inner ear [8-11]. These injuries are referred to as barotraumas. This is particularly true in underwater diving and particularly in freediving, which is performed while breath-holding, because of the limited time available for equalization.

Many maneuvers have been developed to equalize the middle ear pressure during diving. The following are the most popular.

- **Valsalva maneuver**, first described by Antonio Maria Valsalva in 1704 [12], increases nasopharyngeal pressure and creates an active air flow through the Eustachian tube by a forced exhalation against closed nose and mouth.
- **Toynbee maneuver**, described in 1853, produces nasopharyngeal hypertension by swallowing with the nose closed off [11].
- **Marcante-Odaglia maneuver**, also termed the **Frenzel maneuver**, described in 1959 by Duilio Marcante and Giorgio Odaglia [13], creates the same air flow by a nasopharyngeal air compression achieved by moving the tongue upward and backward.

Equalization failures expose the diver to barotraumatic damage of the middle and/or inner ear. At least three middle ear barotrauma staging systems have been proposed: the Teed, the Modified Teed, and the O'Neill

Table 1: Equalization Problems (EP) score

perfect equalization	0
equalization possible and effective but slight difference between the ears (no middle ear barotrauma reported even after many dives and/or many days of diving)	1
equalization possible but ineffective (middle ear barotrauma after few dives)	2
equalization not possible	3

grading systems, with the TEED as the most popular [14-18]. Inner ear barotrauma occurs when pressure variations in the middle ear cleft are transmitted to inner ear structures with the occurrence of a perilymph fistula, intralabyrinthine membrane tear, inner ear hemorrhage and other rarer pathologies.

Differently from barotrauma, a specific staging system for equalization efficiency and disorders does not exist even though equalization problems are very common in divers, with a prevalence of 4.1-91% [16]. In 2012 an English-language questionnaire to assess Eustachian tube dysfunction was validated by McCoul, et al.: the Eustachian Tube Dysfunction Questionnaire (ETDQ-7) [19]. The ETDQ-7 is made of seven questions about more common Eustachian tube dysfunction symptoms, with a score ranging from 1 to 7 for each question [19]. Even though the ETDQ-7 seems to be a good tool to assess Eustachian tube dysfunction in the general population, it is not as useful for assessing problems in diver equalization since it considers symptoms that are present in everyday life and not just during a particular activity such as diving. When administered to divers the ETDQ-7 is therefore inconclusive.

Normally divers are categorized as "good" or "effective" equalizers when they did not report barotrauma and as either "bad" or "ineffective" equalizers or as affected by Eustachian tube dysfunction when they do report it. We think it is useful to divide equalization efficiency into different levels in order to connect each level to a specific risk of barotrauma and evaluate treatment efficacy in improving equalization capability. For this reason, we propose a new scoring system to categorize and assess diver equalization problems and aim to evaluate its reliability. We have termed it the EP score assessment (for equalization problems).

METHODS

From October 2016 through May 2018 we considered a population of 40 Italian freediving breath-holding spearfishermen. All patients were amateurs who had made dives at least twice a week all year long. Exclusion criteria were age younger than 18 and older than 65, clinical evidence or history of ENT pathology and impossibility to follow up with the patient and/or to collect a detailed diving and medical history.

We subdivided our population in two groups: Group A comprised 20 freedivers affected by middle ear equalization disorders (equalization not possible or laborious, impossibility of performing more dives during the day or of diving for more days in row, etc.) on one side and a history of multiple middle ear barotrauma requiring medical treatment for at least one year but without any symptom (hearing loss, fullness, tinnitus, pressure or ear pain, cracking or popping sounds during swallowing, etc.) in everyday life. Group B was composed of 20 healthy freedivers without any history of equalization difficulties or barotrauma. After receiving traditional medical therapies (oral and/or intravenous antibiotics and steroids) and insufflation therapy (Politzer, catheter insufflation, Otovent®) without improvement of equalization difficulties, all the patients in Group A underwent surgery by balloon dilation of the cartilaginous portion of the Eustachian tube of the affected side. Both groups of patients were evaluated with a very detailed interview and a complete ENT examination.

The study participants had various tests performed, including: hearing, tympanometry, acoustic reflexes, tympanometric assessment of Eustachian tube function via nine-step inflation/deflation, as well as completing an ETDQ-7 questionnaire.

The patients were administered the EP score assessment and, concerning Group A patients, just the EP score of the affected side was considered. The EP score was rated as:

- 0 when equalization was perfect and no barotrauma was reported;
- 1 when equalization was possible and effective (no barotrauma reported even after many dives and/or many days of diving) but there was a slight difference between the ears;
- 2 when equalization was possible but ineffective with multiple middle ear barotrauma reported;
- 3 when equalization was not possible (Table 1).

Table 2

	GROUP A				GROUP B		
	Age	Sex	Pre-op EP score	Post-op EP score	Age	Sex	EP score
1	43	M	2	0	29	M	1
2	38	M	2	0	57	M	0
3	28	M	3	3	25	M	1
4	46	M	2	1	30	M	1
5	52	M	2	1	39	M	0
6	46	M	2	0	44	M	0
7	42	M	2	2	43	M	0
8	37	M	2	0	53	M	0
9	38	M	2	2	52	M	1
10	26	M	3	1	25	M	0
11	36	M	2	0	42	M	0
12	38	M	2	1	39	M	1
13	60	M	2	0	28	M	0
14	48	M	2	0	46	M	0
15	25	M	2	1	44	M	1
16	48	M	2	2	38	M	0
17	27	M	2	0	23	M	1
18	22	M	3	0	37	M	0
19	29	M	2	2	29	M	0
20	37	M	2	0	23	M	0

Group A: Freedivers affected by equalization problems
Group B: Freedivers without any history of equalization problems

A statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) package (version 24.0). Continuous variables were expressed as mean and standard deviation. Comparisons between groups were performed by means of the Mann-Whitney U test. The strength of the correlation was tested using the Spearman's rank correlation test. The level of significance accepted was $p < 0.05$.

RESULTS

Group A comprised 20 male freedivers with a mean age of 38.3 years, with a standard deviation of 10.06; Group B comprised 20 male freedivers with a mean age of 37.3 years with a standard deviation of 10.4. Data are homogeneous regarding sex and age. All subjects of both groups showed no pathology at clinical evaluation and audiological tests (nothing to report at clinical examination, bilateral type "A" tympanogram, acoustic reflexes normally present, no dysfunction at the nine-step inflation/deflation test). The ETDQ-7 questionnaire scored in a range of 7-14.4, a normal value, without statistically significant differences between the two groups.

EP score values were very different between the two groups, however. In Group A three patients scored 3 and 17 patients scored 2, while in Group B seven patients scored 1 and 13 patient scored 0 (Table 2). The mean score in Group A was 2.5, while in Group B it was 0.35. The statistical analysis of the data using the Mann-Whitney U test showed a statistically significant difference among the two groups (Z-Score = -5.396 at $p < 0.05$). Group A patients underwent balloon dilation of the Eustachian tube. Fifteen showed improvement or resolution of their equalization problems, with stable results up to three years. Ten patients reported a complete disappearance of the problem, showing a postoperative EP score of 0, and five patients reported an improvement, with persistence of a slight equalization delay on the treated side and showing a postoperative EP score of 1. Five patients did not report any improvement: four of them had a preoperative EP score of 2, and one had a preoperative EP score of 3. The EP scores of these non-responders did not change.

The statistical analysis performed by the Mann-Whitney U test showed a statistically significant difference between EP score before and after surgery (U-value = 42.5 and Z-Score = 4.247 at $p < 0.05$). No statistically significant difference was found between the EP scores of Group A patients who reported good results after balloon dilation and Group B patients (U-value=152.5 and Z-Score=-1.271 at $p < 0.05$). The result, therefore, is not significant.

DISCUSSION

Underwater diving has become increasingly popular around the world, and with its growth the frequency of related pathology has increased. A good equalization technique and capability is the prerequisite for every dive. This is especially true for freedivers who have just a one breath per diving time. For them equalization is performed very quickly, without the possibility to stop the dive temporarily and repeat a failed equalization maneuver. Moreover, freedivers dive multiple times each day for many hours in a row and stress their equalization apparatus considerably.

Equalization disorders are common in divers and are very difficult to assess, especially in freedivers. In the majority of the cases, patients complaining of this problem are completely asymptomatic in everyday

life and do not show any signs at clinical examination, conventional audiological tests or through the ETDQ-7 questionnaire. Regarding the ETDQ-7, normal values in divers with equalization problems and multiple barotraumas in their history are explained by the fact that this questionnaire assesses steady symptoms present in the last month and not just during or after a particular activity such as diving. A diver with equalization problems is usually forced to reduce the frequency of his diving: It is therefore clear that if he did not have a barotrauma in the last month, he is symptom-free with a normal ETDQ-7. This at least was the case with our patients.

A scale specifically suited for equalization disorders that, to the best of the authors' knowledge is not found in medical literature, is therefore needed to allow separation of divers in different groups and to evaluate the success of medical and/or surgical treatment in those individuals complaining of difficulties in equalization.

Even if our study considers a relatively small population of spearfishermen and if additional studies in different and larger populations are necessary to definitely validate the usefulness of our scoring system, the EP score assessment we describe in this paper seems to be a good tool since our data show substantial statistical differences between healthy freedivers and freedivers complaining of equalization disorders and do not show a statistical difference between healthy freedivers and patients treated successfully.

CONCLUSION

This work, even with its limits, demonstrates that the EP score assessment could be a reliable tool to quantify equalization disorders during freediving and to evaluate how the difficulty varies over time and after treatment. Since equalization disorders could be present also in different populations such as scuba divers, fliers, patients undergoing hyperbaric therapy, and others, the EP score could be applicable not only to freedivers but to other populations as well.

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Conflict of interest

The authors declare no conflict of interest exists with this submission.

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RESEARCH ARTICLE

Percutaneous closure of patent foramen ovale for the secondary prevention of decompression illness in sports divers: mind the gap

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ABSTRACT

Objective: To evaluate the efficiency of percutaneous patent foramen ovale (PFO) closure on the recurrence of decompression illness (DCI).

Design: Retrospective, observational study with interview and questionnaire

Setting: Tertiary referral center.

Population: 59 scuba divers with a history of DCI who received a percutaneous PFO closure.

Main outcome measurements: Questionnaire about health status, dive habits and recurrence of DCI after PFO closure.

Results: A total of 59 divers with DCI were included. The most common manifestations of DCI were cutaneous or vestibular DCI. Procedural complications occurred in four patients but none with long-term consequences. Four patients had recurrence of DCI after closure during a 10-year follow-up. In three of these cases there was residual shunting, all of which were initially considered closed. The fourth patient had aggravating factors for his recurrent DCI. A quarter of the patients stated to have changed their diving habits. Four patients quit diving.

Conclusion: Percutaneous PFO closure for secondary prevention of DCI is associated with few, but not negligible, complications. As a large portion of our cohort changed their diving habit after closure it is difficult to ascertain the efficiency of PFO closure for secondary prevention of DCI. However, the study shows that PFO closure does not fully protect against DCI, emphasizing that the relationship between PFO and DCI is but an association. As such it is imperative that divers be counseled to ensure they understand the risks as well as the benefits of percutaneous PFO closure in their specific case.

INTRODUCTION

The presence of a patent foramen ovale (PFO) has been associated with several disease processes including cryptogenic stroke, migraine headache with aura, platypnea-orthodeoxia syndrome, shunt-induced cyanosis and peripheral embolism. Since 1986 a cardiac right-to-left shunt has also been associated with decompression illness (DCI) [1], and an increased risk for DCI in divers with a PFO has since then been reported repeatedly [2-4].

DCI is caused by the formation and growth of inert gas (usually nitrogen) bubbles in the body that result from too rapid a reduction of pressure. While submerged, the body is subjected to increased pressure. This increase in pressure results in saturation of tissues with inert gas, proportional to dive duration and depth. During and after ascent from the dive (decompression), the stored inert gas from the tissues diffuses into the venous system and often leads to bubble formation. These bubbles are small, usually relatively few in number, and do not give rise to any symptoms since they are trapped by the pulmonary capillaries and thus filtered out of the circulation.

However, in cases of a too-rapid reduction of pressure, these bubbles may become so abundant that they can overwhelm the pulmonary filter and make their way into the arterial circulation [5]. Furthermore, bubbles may bypass the lung filter through a right-to-left shunt such as

KEYWORDS: patent foramen ovale; PFO, decompression illness; DCI; percutaneous closure

a PFO and cause arterialization of bubbles or so-called paradoxical embolism [1,6,7]. In that case, even lower degrees of decompression bubbles could then result in DCI, with symptoms based on location and volume of bubbles, such as pain, vertigo, rash or, worst case, paralysis.

From retrospective and case-control studies, the risk of DCI in divers with PFO has been estimated to be two to five times higher than divers without a PFO. However, recreational diving within currently recommended safe diving practices has a low overall risk of approximately 1/4,000 dives [5,8,9]. Even with the increased risk, only a very small portion of divers with PFO will ever experience DCI. Therefore, baseline PFO screening in divers is not recommended by diving-related scientific societies [10]. Diagnostic evaluation for PFO after DCI is recommended in case of severe or repetitive DCI with cerebral, spinal, vestibulocochlear or cutaneous manifestations, especially in the absence of provocative features (such as a severe decompression or bubble-prone dive) [10-12].

Suggested recommendations for divers with diagnosed PFO after DCI include the cessation of diving, adopting a more conservative diving profile, or PFO closure. While percutaneous closure of PFO seems to gain acceptance for the secondary prevention of young cryptogenic stroke [13], controversy still exists regarding closure of PFO after DCI. There might be a role for percutaneous PFO closure, especially for large PFOs. However, current evidence on the efficacy of percutaneous closure of PFO for the secondary prevention of recurrent DCI in divers is inadequate in quality and quantity. Although percutaneous closure of PFO has been used for a number of years, rather indiscriminately, to reduce the risk of DCI, the rate of DCI recurrence after closure has not well been established. This is important because even though percutaneous PFO closure is perceived as a relatively safe procedure, it is associated with a low – but not negligible – risk of complications, including vascular injury, cardiac perforation, air embolization during implantation, device embolization, early and late thrombosis, and atrial arrhythmias [14]. Therefore, the aim of this report is to summarize data for evaluation of the efficiency and safety of percutaneous PFO closure on the secondary prevention of DCI, in a Belgian divers' cohort over a 10-year period.

METHODS

All patients with a diving-related DCI event who underwent percutaneous PFO closure between 2007 and 2016 in the University Hospital of Antwerp were included. Only patients who received the Occlutech® Figulla® Flex II PFO device (the most-used PFO occluding device in this center) were selected for further analysis. Based on medical file review the following data were collected: patient demographics, type of DCI, number of DCI events before PFO closure, diving habits, procedural complications, and recurrence of DCI after closure. In all patients the presence of PFO with right-to-left shunting was diagnosed with contrast transesophageal echocardiography (c-TOE) and performance of the Valsalva maneuver. The contrast solution, shaken gelofusine, was injected into the left median cubital vein. All c-TOE procedures were performed with the patient sedated, using 1mg of midazolam IV, and local anesthetics. In all patients, the percutaneous PFO closure procedure was performed with the patient under general anesthesia, via femoral venous access. Short-term follow-up consisted of a transthoracic echocardiography (TTE) the day after PFO closure.

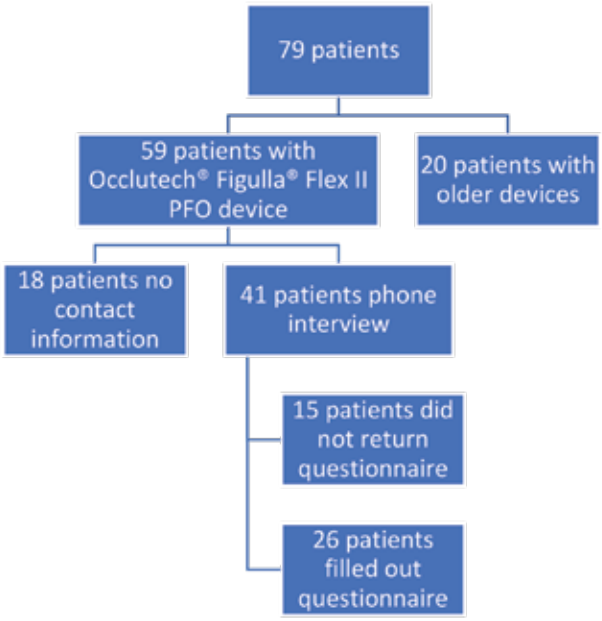
Evaluation of the PFO closure was performed with c-TOE at three months if the patient was a professional diver, and at six months for recreational divers. In case of residual shunting a control c-TOE was performed at three-month intervals until closure or up to 12 months after the percutaneous intervention. All patients were contacted in September 2017 by phone for an interview and asked to fill out a dedicated questionnaire to gather data about long-term follow-up.

RESULTS

A total of 79 patients who had a percutaneous PFO closure after experiencing DCI were identified (Figure 1). In 20 of these 79 patients, devices that are no longer being manufactured were used; consequently, these patients were excluded for further analysis since these older devices are known to have higher rates of residual shunting and procedural complications. Thus 59 divers whose PFO was closed with an Occlutech Figulla Flex II PFO device were included. Forty-one divers received a telephonic interview and were asked to fill out a dedicated questionnaire to obtain specific dive-related information, which 26 out of 41 patients completed. Patient demographics can be found in Table 1. Eighteen patients could not be reached, and information was gathered by contacting their family physician. Median follow-up was 65 months (18-108 months, interquartile range /IQR 39 months).

Average patient age at time of closure was 41 years (17-65 years, SD 11.5 years). Our population has a male predominance of 72%. Mean body mass index (BMI) was 26.33 (19.95-35.80 kg, SD 3.4 kg). The majority of our patients included recreational divers. There were six

Figure 1: Inclusion flowchart



professional divers. The median diving experience for our population was 11 years (4-50 years, IQR 12 years) and the median number of dives was 466 dives (14-3,900 dives, IQR 544 dives). All patients experienced at least one DCI event before the procedure; 20 patients (33%) experienced more than one event. All DCI events were reported to have followed dives consistent with safe decompression policies, although this could not be verified (dive profiles not available and rarely the original medical report regarding the DCI). Post-hoc review of symptoms and dive profiles, whenever available, cast doubt on one reported DCI event; all other events were likely correctly diagnosed. Out of all reported events, 63% presented with cutaneous manifestations, 35% with vertigo and dizziness and 15% with cerebral events such as motor and sensory neurologic dysfunction. In 16% of the patients there was a combination of different DCI types. About half of the events (46%) occurred after consecutive dives. In all cases the PFO was considered significant (>30 bubbles). In 40 patients (68%) there was shunting in rest, while in 19 patients (32%) there was significant shunting only after Valsalva maneuver. There were no cases of atrial septal defect or cribriform septa.

Table 1: Overview of patient characteristics

CHARACTERISTIC	OUTCOME
gender	
female	27%
male	73%
biometrics	
mean BMI	26.33 (19.95-35.80)
mean height	1m77 (1m59 -1m92)
cardiac risk factors	
diabetes	0%
smoking	24%
hyperlipidaemia	30%
hypertension	17%
diving experience	
professional diver	10%
recreational diver	90%
median diving experience (years)	11 years (4-50 years)
median diving experience (number of dives)	466 (14-3900 dives)
type of DCI prior to closure	
cutaneous	63%
vestibular	35%
cerebral	15%
combination	16%
mean age at PFO closure	41 years (17-65 years)

Procedure and complications

A total of 57/59 procedures (96%) were considered successful. In two cases, there was malposition of the device, with one needing revision with a second occluder device. Complications occurred in four patients (7%). There were no life-threatening complications. Complications included one arteriovenous fistula in the right femoral artery needing surgical treatment; one case of a pseudoaneurysm (successfully treated with thrombin injection) in combination with an arteriovenous fistula in the right femoral artery, which was treated conservatively; and two cases of paroxysmal atrial fibrillation (AF) who received pharmacological reconversion with no recurrence of AF afterwards. All complications presented within six months of the procedure. There were no long-term consequences to these complications.

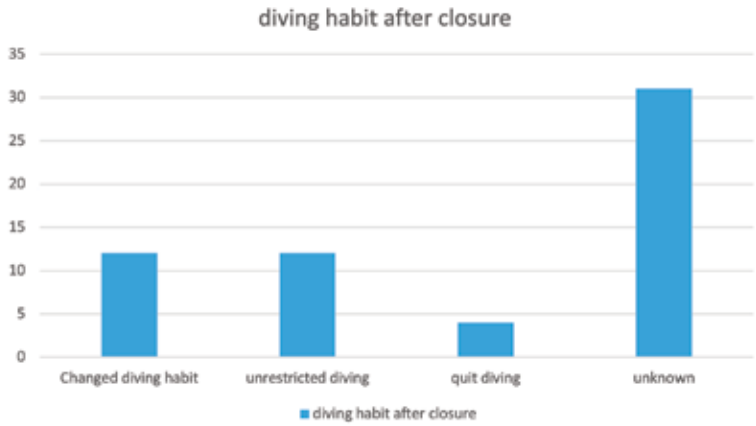


Figure 2: Diving habits after closure. Changed diving habit includes those that elected to dive more conservative and those that changed to diving with nitrox.

Residual shunting

In nine patients (15%) there was still residual right-to-left shunting at one year. However, in only two patients (3%) was this considered significant (>30 bubbles). The other seven patients (12%) had minimal residual shunting (<5 bubbles) and were therefore considered closed. In one case, opacification of the left atrium was seen after more than five heartbeats, but there was no visualization of shunting over the occluder device and thus, the PFO was considered closed. This was not present before and during his PFO closure, which makes lung shunting highly unlikely. No explanation was found for this finding. The diver in question has performed 120 uneventful dives since his closure, albeit adhering to more conservative diving profiles. The majority of the control c-TOEs were done by three cardiologists experienced in PFO imaging, with a minority (<5%) of the c-TOEs done by other cardiologists and cardiologists in training.

Return to diving

The mean time between the intervention and return to diving was six months (three months to 12 months, SD two months). A total of 6,865 post-closure dives were reported by 26 patients (Median 235 dives, IQR 312 dives). A quarter of the patients stated to have changed their diving habits: 10 patients chose to dive more conservatively (<30 meters in depth, no consecutive dives, no-decompression diving only); two patients switched to diving with nitrox (nitrogen/oxygen gas mixture with an oxygen concentration higher than the usual 21%) instead of air; and four patients quit diving altogether (Figure 2). None of these patients had recurrence of DCI on a total of 2,528 dives (Median 120 dives, IQR 450). Of the four who quit diving, two did so because of persistent residual shunting after PFO closure; one had developed a fear of diving, and the last one "took a break" from diving and did not (yet) restart.

Recurrence of DCI

In four patients, there was a new DCI event after PFO closure (Table 2). The first patient presented with recurrent DCI within three months after diving restriction was lifted (seven years prior to interview). This patient presented with identical symptoms (cutaneous DCI) compared to his pre-closure status after an air dive > 30 msw. It appeared subsequently that his PFO was never fully closed due to malposition of the occluder device. This patient has quit diving since then. The second patient also presented with identical DCI symptoms (cutaneous) within three months after diving restriction was lifted (three years prior to interview). Symptoms presented after an uneventful rebreather dive (70 msw, one hour) while adhering to decompression tables. He was considered closed at six months but control c-TOE after the event showed some residual shunting after Valsalva maneuver (10 bubbles). His current diving status is unknown. Of note, in both cases the c-TOE upon which PFO closure was confirmed was performed by a cardiologist in training. The third patient, a professional diver, presented with identical DCI lesions (cutaneous) four years after closure (four years

Table 2: Patients with recurrent DCI after PFO closure

Patient	1	2	3	4
c-TOE at 6 months after closure	significant shunting	minimal shunting	significant shunting	no shunting
c-TOE at 9 months after closure	no shunting	no shunting	no shunting	/
timing DCI after resuming diving	3 months	3 months	4 years	4 and 5 years
C-TOE after event	significant shunting	minimal shunting	significant shunting	no shunting

Note: Patient 4 had bubbles prone diving profiles that can explain his recurrent DCI events.

prior to interview). This event presented after a dive of 40 msw, 45 minutes with surface decompression, in accordance with the Netherlands Diving Center (NDC) decompression tables. He was considered closed at one year, but control c-TOE after the recurrence of DCI showed massive right-to-left shunting (>30 bubbles) after Valsalva. Most likely this patients PFO was never fully closed [15]. He refrained from a revision of the PFO closure and has quit diving. The fourth patient presented respectively two and three years after closure with new DCI events (one and two years prior to interview), but the symptoms were different from the DCI prior to his PFO closure. The first event presented after a consecutive dive to 30 msw for total duration of 30 minutes, with the first dive of the day performed at 54 msw for 40 minutes anda decompression stop at 12 msw. The second event presented after a comparable diving profile – i.e., a consecutive dive with depth and timing comparable to the first event. As these were bubble-prone dive profiles, there were factors considered aggravating for both DCI episodes after his PFO closure, and his new DCI events were considered not necessarily PFO-related. His control c-TOEs after both DCI episodes showed no residual shunting. This patient is currently an active diver (686 dives since PFO closure).

DISCUSSION

This study aimed to evaluate the efficiency of percutaneous PFO closure for secondary prevention of DCI. In our cohort, we found that four divers (6%) presented with recurrent DCI after percutaneous PFO closure. Of these four cases, three were found to have residual shunting after percutaneous closure of their PFO while being considered closed. Further, in two cases these examinations had been done by inexperienced cardiologists. This confirms the need for accurate assessment of any residual shunting after PFO closure as we have described before [15]. According to the joint position statement on PFO and diving [10], a repeat bubble contrast echocardiogram is required to confirm shunt closure before returning to diving. c-TOE in combination with Valsalva is traditionally viewed as the most reliable maneuver for assessment of PFO closure. However, the use of sedation makes the performance of the Valsalva maneuver more difficult [16-18], resulting in higher rates of false negative results, especially in case of smaller shunt [5,19]. This likely explains the three false negatives in our study. Other maneuvers have been proposed to address this problem such as abdominal compression, inferior vena cava compression, cough, sniff, and modified Müller (rapid forceful nasal inspiration) and have shown promise but require further investigation [20]. Alternatively, the Valsalva maneuver can be performed more easily during contrast transthoracic echocardiography (c-TTE) imaging, which has been shown to be comparable to c-TOE for specificity and sensitivity [21,22]. Therefore, c-TTE might be better suited for post-procedural evaluation of residual shunting. However, this remains to be determined in future studies.

Procedural complications were infrequent in our cohort, consistent with the literature [23]. Although there were no long-term consequences, these complications are not negligible and are a cause of distress in patients. This is important, especially when considering the current uncertainty around the efficiency of PFO closure for secondary prevention of DCI [12,24]. According to the previously mentioned joint statement, percutaneous PFO closure should be considered if the patient is unwilling to stop diving and/or if the dive profiles cannot be changed [10]. In addition, the UHMS Best Practice Guidelines state: "*Data*

to suggest PFO closure prevents DCS are incomplete and if it is suspected that a diver's repetitive DCS incidents are related to a PFO, reduction of decompression stress in future diving activities by more conservative diving practice is probably a better approach than PFO closure" [12]. As such it can be debated whether PFO closure was truly necessary in our cohort of mostly recreational divers. Indeed, Klingmann, et al. [25] reported a reduction from 34 to four events of DCI before and after adoption of more conservative dive profiles. Even more recently a study of 77 divers with PFO closure for DCI showed that a conservative dive profile was safe in those who refrained from PFO closure [26]. Thus, thorough counseling of divers with PFO or other right-to-left shunts as to the mechanisms of decompression bubble occurrence and shunting of bubbles through the PFO appears to be equally effective in reducing both the number of detectable bubbles and the incidence of DCI [25,27,28]. To date there is only one published trial evaluating prospectively the effect of PFO closure in recreational divers [29]. In this study, three groups of divers were followed up after DCI with subsequent investigation for the presence of a PFO: a group that did not have a PFO (39 divers); a group that chose not to have their PFO closed (39 divers); and a "closure" group (26 divers). After a follow-up period of a little more than five years and approximately 50 dives per year, a significant reduction in DCI recurrence was found in divers who had their PFO closed, compared to those who did not. It appears that the divers who had selected not to have their PFO closed did not make significant changes to their diving behavior. However, divers who did have their PFO closed still had a higher follow-up incidence of DCI compared to divers with no PFO. This may indicate a renewed "sense of security" resulting in a riskier diving behavior. Furthermore, even if the differences were statistically significant, there were only four DCI events in the "no-closure" group and one event in the PFO closure group, making statistical bias at least possible (if one more diver in the PFO closure group would have "admitted" to a new DCI event, all statistical significance would be lost).

In our population 25% of those who filled in the questionnaire stated to have changed their diving habits, even though their PFO was closed. It is possible that even a higher proportion of our population changed their way of diving, as only 44% of our patients returned the questionnaire describing their diving habits after PFO closure. Also, as it is impossible to quantify how many and how much participants' diving has been changed following the procedure, our findings must be interpreted with caution. Possibly half our population might have changed their diving habits, and even if not, this change in diving habits precludes any definite evaluation of the efficiency of PFO closure on the occurrence/recurrence of DCI. From a pathophysiological point of view, the most effective strategy to prevent DCI is by reducing "diving exposure." One must remember that DCI is caused by inert gas bubbles, and that closure of a PFO does not fully protect divers from DCI if significant numbers of gas bubbles are present after a dive. Moreover, DCI may still be caused by locally trapped gas bubbles [14], or bubbles that have arterialized through other pathways such as intrapulmonary arteriovenous anastomoses [30].

As such, one can argue that if there was a medical necessity for the recreational divers in our cohort to have had their PFOs closed, as they could easily have resorted to changing their dive profiles. Our observation is, however, that some divers find it very difficult to change their diving habits even after medical advice; to quit diving altogether is usually not an option. As the current evidence on the efficacy of percutaneous PFO closure for the secondary prevention of recurrent DCI in divers is uncertain [24] in combination with few but not negligible complications associated with the procedure, we advocate that patient selection for percutaneous PFO closure should be carried out only by experienced interventional cardiologists, in liaison with clinicians with specific expertise in diving medicine. It is imperative that divers be counseled by diving medicine experts to ascertain that they understand the risk-benefit of PFO closure for secondary prevention of DCI and that modifying their diving behavior is a realistic and feasible option.

LIMITATIONS

Our study has several limitations. First, the follow-up response rate was low, with only 44% of divers completing the questionnaire. As we can assume that in case of a new DCI event after closure the diver would have sought medical attention, it would not have influenced our findings on recurrence of DCI after closure. However, we did lose valuable insight into their diving habits after closure. Secondly, there is an uncertainty in the quality of c-TOE to assess residual shunting. Therefore, this study does not allow us to make definite assumptions about the efficiency of PFO closure in secondary prevention of DCI. However, this study shows the importance that the decision for PFO closure in prevention of secondary DCI should be an interdisciplinary process and that, when closure is decided upon, thorough evaluation is mandatory to ascertain closure success.

CONCLUSIONS

Although closure success and complication rate seem in line with previously reported data, uncertainties in the evaluation of complete closure and continuing to dive "bubble-prone" dive profiles are likely responsible for a non-negligible number of recurrent DCI (four out of 55 divers who continued diving after PFO closure). Even though the post-closure DCI incidence rate cannot be estimated in this study, as we have no precise data on the number and type of dives performed after closure, it does illustrate that the relationship between PFO and DCS is an association: Not all DCS is due to the presence of a PFO, and closure does not uniformly prevent it. Therefore, we should ensure that divers understand the uncertainties about the efficacy of transcatheter closure of a PFO and the possibility of complications [27]. This implies a multidisciplinary approach with evaluation and counseling, not only by a cardiologist but also by an experienced diving medicine specialist. The divers should understand that modifying diving behavior is a realistic and feasible option. They should have the statistics of DCI risk in diving versus the risk of complications of PFO closure explained, and to be cautioned that there is no formal medical indication to close the PFO solely for diving. If PFO closure is discussed, this should be assessed and decided only on a case-by-case basis followed by adequate assessment of the PFO closure to confirm there is no or little residual shunting.

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Disclosure statement

The authors report no conflicts of interest.

Ethics

This study has been approved by the Ethics Committee of the University Hospital of Antwerp under registration number B300201835468

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SHORT COMMUNICATION

Gas in coronary artery: A case of fatal decompression sickness evaluated by computed tomography

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ABSTRACT

A 54-year-old man suffered a leg cramp while diving in the ocean at a depth of 20 meters. He began to surface, with his ascent based on a decompression table. He lost consciousness at the surface and was rescued by a nearby boat. The boat staff judged him to be in cardiac arrest, so they performed chest compressions. When the boat reached port where an ambulance was waiting, emergency medical technicians confirmed that the patient was in cardiac arrest; his initial rhythm was asystole. Treated with basic life support, the patient was then transported to a rendezvous point, where a physician-staffed helicopter waited. The patient remained in cardiac arrest, so the staff of the helicopter performed tracheal intubation with mechanical ventilation, securing a venous route, infusion of adrenaline, and mechanical chest compression. On arrival at our hospital 100 minutes after collapse, he remained in cardiac arrest. Continued advanced cardiac life support failed to obtain spontaneous circulation. Whole-body computed tomography (CT) at 120 minutes after the collapse showed multiple gas bubbles in the heart, aorta, inferior vena cava, cerebral artery, coronary artery and portal vein with lung edema. This is the first case to show gas in the bilateral coronary arteries on CT. The present case clearly demonstrates that decompression sickness can also induce acute coronary syndrome.

INTRODUCTION AND TREATMENT

A 54-year-old man suffered a leg cramp while diving in the ocean at a depth of 20 meters. He began to surface, with his ascent based on a decompression table but lost consciousness at the surface. He was rescued by a nearby boat. The boat staff judged him to be in cardiac arrest, so they performed chest compressions.

When the boat reached port where an ambulance was waiting, emergency medical technicians confirmed that the patient was in cardiac arrest. His initial rhythm was asystole. Treated with basic life support, the patient was then transported to a rendezvous point, where a physician-staffed helicopter waited. The patient remained in cardiac arrest, so the staff aboard the helicopter performed tracheal intubation with mechanical ventilation, securing a venous route, infusion of adrenaline, and mechanical chest compressions.

RESULTS

On arrival at our hospital 100 minutes after collapse, the patient remained in cardiac arrest. The results of a venous blood gas analysis were as follows: pH 6.564; PCO_2 170 mmHg; PaO_2 8.3 mmHg; HCO_3-14.5 mmol/L; base excess -37 mmol/L; and lactate 29 mmol/L.

Continued advanced cardiac life support failed to obtain spontaneous circulation. The results of a biochemical blood analysis on arrival were as follows: white blood cell count 7,800/μL; hemoglobin 15.9 g/dL; platelet count 7.7×10^4/μL; total protein 7.6 g/dL; albumin 3.9 g/dL; glucose 437 mg/dL; total bilirubin 0.5 mg/dL; aspartate aminotransferase 169 IU/L; alanine aminotransferase 138 IU/L; blood urea nitrogen 20.9 mg/dL; creatinine 1.28 mg/dL; sodium 147mEq/L; potassium 11.1mEq/L; chloride, 102 mEq/L; prothrombin time 21.8 (11.8) seconds; activated partial thromboplastin time 121.0 (26.4) seconds; fibrinogen 45 mg/dL; fibrinogen fibrin degradation product over 960 μg/mL. Whole-body computed tomography (CT) at 120 minutes after the collapse showed multiple gas bubbles in the heart, aorta, inferior vena cava, cerebral artery, coronary artery and portal vein with lung edema (Figure 1).

KEYWORDS: air embolism; coronary artery; decompression illness; resuscitation

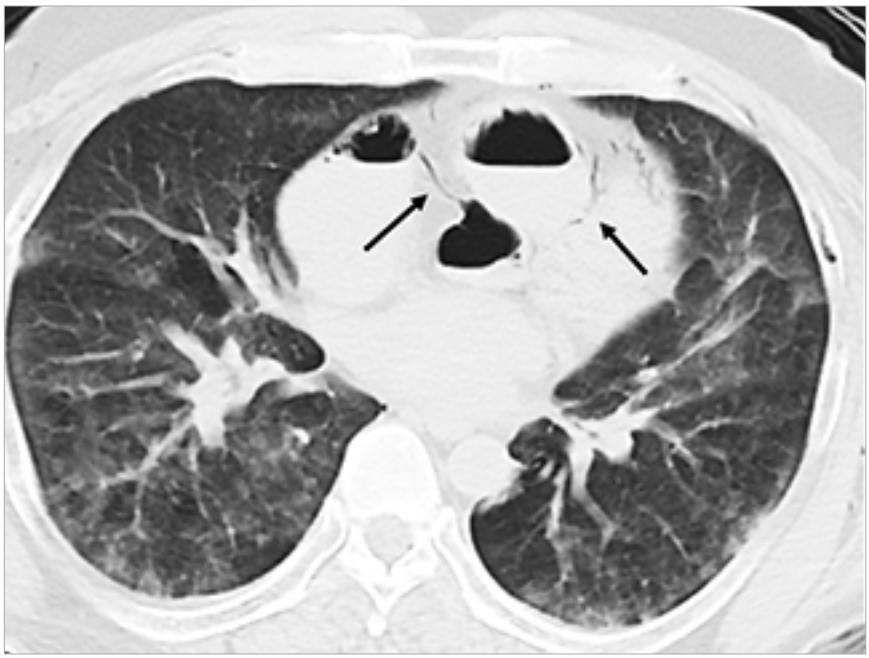

Figure 1: Whole-body computed tomography (CT) at 120 minutes after the collapse. CT shows gas in the heart, aorta and bilateral coronary arteries (arrow).

DISCUSSION

Decompression sickness and arterial gas embolism, collectively known as decompression illness (DCI), are rare but serious afflictions that can result from compressed-gas diving exposure [1]. The present case demonstrated multiple gas bubbles in the vasculature and heart due to decompression sickness. Unfortunately, there have been no reports of patients able to obtain social rehabilitation after suffering cardiac arrest due to decompression sickness.

CONCLUSION

This is the first case to show gas in the bilateral coronary arteries on CT. Acute coronary syndrome can occur while diving [2], induced accidentally by plaque rupture [3]. However, the present case clearly demonstrates that decompression sickness can also induce acute coronary syndrome.

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RESEARCH REPORT

Hyperbaric oxygenation affects acetylcholine-induced relaxation in female diabetic rats

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ABSTRACT

We aimed to assess the effects of intermittent hyperbaric oxygenation (HBO_2 at 2 bars for 120 minutes a day for four successive days) on acetylcholine-induced vasorelaxation (AChIR) in female Sprague-Dawley (SD) rats (N=80) that were randomized into four groups: healthy controls (CTR); diabetic rats (DM); and control and diabetic rats that underwent hyperbaric oxygenation (CTR+HBO and DM+HBO), respectively. AChIR was measured in vitro in aortic rings, with/without L-NAME, MS-PPOH, HET0016 or indomethacin. mRNA expression of eNOS, iNOS, COX-1, COX-2, thromboxane A synthase 1 (TBXAS1), CYP4A1, CYP4A3 and CYP2J3 was assessed by qPCR. Systemic oxidative stress and plasma antioxidative capacity were determined with the thiobarbituric acid-reactive substances (TBARS) and the ferric reducing ability of plasma (FRAP) assays, respectively. There was no significant difference in AChIR among experimental groups of rats. In CTR and DM group of rats, AChIR was mediated by NO and EETs pathway, while in the CTR+HBO and DM+HBO groups, NO-pathway prevailed. iNOS expression was upregulated in the DM group compared to CTR, while HBO_2 upregulated eNOS in CTR group and TBXAS1 in DM group of rats. In both, CTR and DM group of rats, the sensitivity to ACh in the presence of L-NAME or in the presence of MSPPOH was significantly decreased compared to the response to ACh in the absence or presence of indomethacin or HET0016. DM and DM+HBO rats had increased TBARS compared to their respective controls. In conclusion, HBO_2 presumably alters vasorelaxation in response to ACh from NO-EETs mediated pathways to solely NO-pathway, without affecting oxidative status of DM rats.

KEYWORDS: hyperbaric oxygen; diabetes; endothelium; 20-HETE; epoxyeicosatrienoic acids; female rats; nitric oxide; acetylcholine

INTRODUCTION

Diabetes mellitus (DM) has been strongly associated with development and progression of cardiovascular disease (CVD); e.g., diabetic patients exhibit increased incidence of myocardial infarction and stroke, as well as peripheral ulcerations due to tissue hypoxia caused by insufficient perfusion. Among other possible mechanisms, this tissue underperfusion could be explained by altered vascular reactivity of both micro- and macrocirculation [1-4]. Along with altered smooth muscle vascular cell (SMVC) function and advanced glycation of proteins, the disbalance of endothelial mediators (e.g., vasoconstrictors versus vasodilators), as well as increased production of reactive oxygen species (ROS) have been proposed to contribute to diabetic vascular dysfunction, although the exact metabolic pathways and signaling mechanisms are still not fully elucidated [1-3, 5-9]. While most studies have confirmed an attenuated acetylcholine (ACh)-induced and nitric oxide (NO)-dependent vasodilation in diabetic models [1,7,10,11], the contribution of other endothelial vasoactive mediators is less well investigated. Besides NO, the arachidonic acid (AA) metabolites released from the endothelium play an important role in the regulation of vascular tone. The enzymes cyclooxygenase-1 and -2 (COX-1, -2) metabolize AA to prostaglandin G_2 and prostaglandin H_2. These in turn may be converted to various prostaglandins: e.g., prostacyclin (PGI_2), which exhibits vasodilator effect, or to thromboxanes (TXA_2, TXB_2), which act as vasoconstrictors. Under the action of various specific cytochrome P450 (CYP450) enzymes, AA could either be metabolized in epoxidation reactions to epoxyeicosatrienoic acids (EETs), which act as potent vasodilators, or by ω-hydroxylase to 20-hydroxyeicosa-

tetraenoic acid (20-HETE) which cause vasoconstriction [12-14]. Some studies reported involvement of 20-HETE in diabetes-induced vascular dysfunction, while others suggested EETs to be protective against streptozotocin-induced diabetic nephropathy [15] and coronary artery disease [16]. Recently we reported that in male diabetic rats, ACh-induced relaxation (AChIR) of aortic rings was mediated mainly by NO, with contribution of CYP450-produced vasodilators, possibly EETs [17]. Still, the data on CYP450 metabolites and their role in DM remain scarce and inconclusive [2,18,19], especially in the female sex.

One of the adjunct therapies for DM that is particularly efficient in treatment of diabetic ulcerations has been hyperbaric oxygen (HBO_2) therapy [20-22]. HBO_2 increases tissue oxygenation, but more interestingly, it has been implicated in benefiting vascular reactivity by enhancing relaxation of isolated aortic rings and reducing infarct size of isolated hearts [20-22]. Also, upregulation of eNOS, endothelial nitric oxide synthase 3 (NOS), was demonstrated in rat cerebral microvascular endothelial cells under the influence of HBO_2 [20-22]. Some of the metabolites of CYP450 enzymes have been proposed to act as a putative oxygen sensor correlating with tissue pO_2) [23,24]. Thus, it is tempting to speculate that the CYP450 metabolites-dependent vasodilation and/or expression of CYP450 enzymes might possibly be altered by HBO_2 (especially in DM) [20-22]. Indeed, earlier study by our research group has shown upregulation of CYP2J and CYP2C enzymes that catalyze the epoxygenation of AA into EETs in aortic rings of streptozotocin-induced diabetic male rats exposed to intermittent HBO_2 treatment [20-22,25]. In light of available data we hypothesized that HBO_2 might interfere with the endothelium-dependent vasodilation as well as with the synthesis or sensitivity to 20-HETE and/or EETs which, in turn, could have an important effect in restoring vascular function in diabetes.

The aim of the present study was to assess the potential effect of intermittent HBO_2 on vascular reactivity in streptozotocin-induced diabetic female rats with special focus on the role of CYP450 metabolites. We aimed to investigate whether HBO_2 treatment induces changes in vascular reactivity to ACh in isolated aortic rings of diabetic female rats, and to elucidate if potential changes might be due to altered involvement of CYP450 metabolites. To do so, we have performed functional vascular reactivity experiments in the presence and absence of specific CYP450 inhibitors and measured messenger RNA (mRNA) expression of various CYP450 isoforms, respectively.

MATERIALS AND METHODS

Experimental animals

The animals were raised at the animal care of the Faculty of Medicine Josip Juraj Strossmayer University of Osijek, Croatia, which is a registered and certified user/breeder of mice and rats for educational and scientific purposes. All experimental procedures conformed to the European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes (Council of Europe No 123, Strasbourg 1985). The experiments were approved by the Ethics committee of the Ethics Committee Faculty of Medicine, University of Osijek.

A total of 80 female Sprague-Dawley (SD) rats were divided into four groups (n=20 per group):

1) controls (CTR);
2) diabetic rats (DM);
3) controls that underwent the HBO_2 protocol (CTR+HBO);
4) diabetic rats that underwent the HBO_2 protocol (DM+HBO).

Fifteen rats from each group (n=15 per group) were used for functional aortic ring reactivity experiments, and five animals from each group (n=5 per group) were used for the measurement of mRNA expression of enzymes catalyzing vasoactive mediators' synthesis in thoracic aorta tissue. All rats were housed in pairs in shoebox-style cages, with free access to standard rat chow and tap water, and maintained on a 12:12-hour light:dark cycle. Rat weight was measured at the end of the study protocol.

A Type 1 DM model was induced by intraperitoneal streptozotocin (60mg/kg) injection at the age of six weeks. A OneTouch Ultra (LifeScan, Inc., Milpitas, California, U.S.) glucometer and the tail-cut method were used to measure blood glucose levels one week after the streptozotocin injection and again on the day of the experiment (at the age of 12 weeks). All animals that did not develop diabetes at one week after the injection (minimum blood glucose cutoff at the age of seven weeks was 15 mmol/L), or without a confirmed diabetes again at 12 weeks were euthanized and not used in further experiments.

Hyperbaric oxygen treatment

Under the HBO_2 protocol, rats from the HBO_2 groups were treated in a hyperbaric chamber (containing carbon dioxide/CO_2 adsorbent) with 100% oxygen (using a pressure of 2 bar) for 120 minutes a day for four successive days (with the addition of 15 minutes for compression phase and 15 minutes for decompression phase) during

four consecutive days (Recompression Chamber for Experiments 110L, Djuro Djakovic, Aparati d.d., Slavonski Brod, Croatia) [17].

Surgery, aortic rings acquisition and assessment of aortic ring reactivity to acetylcholine

General procedures for aortic rings experiments were done according to the protocol already described in our laboratory [17,26]. A day after HBO_2 treatment (at the age of 12 weeks, after a six-week DM duration) the aortic rings experiments were conducted. The rats were anesthetized with a combination of ketamine (75mg/kg) and midazolam (2.5mg/kg), and decapitated with a guillotine. The descending thoracic aorta was dissected from the connective tissue, placed in an oxygenated modified Krebs-Henseleit solution, and cut into short segments (rings) of about 3-4 mm in length (N=4 rings per n=1 thoracic aorta). These rings were then mounted in tissue bath chambers containing Krebs-Henseleit solution (maintained at 37°C) that was oxygenated with 95% O_2/5% CO_2 compressed gas mixture. Passive tension for each ring was set at 2.0 grams (g). Intactness of endothelium was tested by precontracting the rings with 10^{-7} molar concentration (M) (final concentration) noradrenaline (NA) and inducing relaxation with 10^{-5} M ACh. Rings that failed to relax were not used for further studies. After the initial test for vessel viability and endothelial integrity, maximal contraction was induced with 60 mM KCl + 10^{-7} NA.

After this phase, in the AChIR protocol aortic rings were precontracted with 10^{-7} M NA for five minutes, and cumulative concentration-response curves to ACh were obtained by adding ACh of increasing concentration to achieve the final bath concentration of 10^{-9} to 10^{-5} M ACh. AChIR protocol was used in the absence and in the presence of the corresponding inhibitor:

1) the eNOS inhibitor, nitro-L-arginine methyl ester (L- NAME, $3x10^{-4}$ M);
2) non-selective COX-1 and COX-2 inhibitor, indomethacin (10^{-5} M);
3) the selective EETs epoxidation inhibitor, N-(methyl sulfonyl)-2-(2-propynyloxy)-benzenehexanamide MS-PPOH (10^{-5} M) that inhibits the formation of arachidonate 11,12-epoxides by CYP4A2 and CYP4A3 enzymes; and
4) the selective inhibitor of 20-HETE formation, N-hydroxy-N'-(4-n-butyl-2-methylphenyl)-formamidine (HET0016, 10^{-5} M) in tissue bath.

Before adding any increasing concentration of ACh, aortic rings were incubated for 10 minutes with the corresponding inhibitor. The amount of relaxation was expressed as the percentage of the remaining contraction of the NA-induced vasoconstriction.

Oxidative stress measurements

Blood samples were collected from the decapitation site, centrifuged at 3,500 rpm for 10 minutes, and serum samples were stored at -80 °C. Experiments were performed according to the protocol that was already described in our laboratory [27]. As a direct indicator of oxidative stress, the spectrophotometric thiobarbituric acid reactive substances (TBARS) method was used for measuring the products of lipid peroxidation with malondialdehyde (MDA) as standard (μmol l–1 MDA). The products bind to a thiobarbituric acid (TBA) at low pH. Since the method is non-specific because other substances also bind to a TBA (including proteins), trichloroacetic acid (TCA) was first added to the sample to precipitate the proteins, and after that the supernatant was used for the measurements [28]. The absorbance of the sample was measured at 572 and 532 nm.

Antioxidant capacity was assessed using the ferric reducing ability of plasma assay (FRAP). Fe^{3+}-TPTZ (2,4,6-tris(2-pyridyl)-s-triazine) is reduced to Fe^{2+}-TPTZ in the presence of antioxidants; blue discoloration occurs. The absorbance of the sample was measured at 593 nm (Nanophotometer P300 UV/VIS, IMPLEN), using trolox as a standard (mmol trolox) [29].

mRNA expression of enzymes catalyzing vasoactive mediators in rat aorta

Quantitative real-time PCR was used to detect expression levels of eNOS and inducible nitric oxide synthase (iNOS), COX-1, COX-2 and thromboxane A synthase 1 (TBX-AS1), CYP4A1, CYP4A3 and CYP2J3 in all four groups of female SD rats. An aorta sample for each rat was placed in RNA later (Qiagene, Germany) and stored at –80 °C. RNA isolation from tissue homogenate was made with TRI reagent (Life Technologies, U.S.) according to the protocol used/developed by Chomczynski and Sacchi [20]. Isolated and dissolved RNA was stored at -80°C. RNA integrity was checked on 1% agarose gel, and concentration was measured with NanoDrop 1000 spectrophotometer. cDNA was made with the High Capacity Reverse Transcriptase kit (Applied Biosystems, U.S.) under conditions determined by the protocol. Gene expression was normalized to the expression of the housekeeping gene HPRT and further analyzed. Expression determination of all genes was measured on the real-time PCR Bio Rad CFX96.

Table 1. Sequences of custom-made primers for determination of mRNA expression

mRNA	Primer sequence	PCR product length (bp)	Annealing temperature (°C)
HPRT	For -5'-GAAAGAACGTCTTGATTGTTGAAGATAT-3' Rev - 5'-GAGAGGTCCTTTTCACCAGCAA-3'	129	59
COX-1	For - 5`-TCCTGTTCCGAGCCCAGTT-3` Rev - 5`-GCCAGTGATAGAGGTGGTTGAAT-3`	69	61
COX-2	For - 5`GAAAGAAATGGCTGCAGAGTTGA 3` Rev - 5`GCAGGGCGGGATACAGTTC 3`	71	63
TBXAS1	For - 5'-CTGAGGAAGTTGGGCATCAGA-3' Rev - 5'-CCTGGCGGAAAAACATCAA-3'	70	57
eNOS	For - 5`-CGAACAGCAGGAGCTAGAGG-3` Rev - 5`-GAGGTGGATCTCTCCTGGGT-3`	211	64
iNOS	For - 5`-TGGTGAGGGGACTGGACTTT-3` Rev - 5`-CCAACTCTGCTGTTCTCCGT-3`	101	63
CYP2J3	For - 5'-CCTTTCTGTTCCTGGCTGATTT-3' Rev - 5'- AGGCCCTGGCGGGTAGT-3'	62	60
CYP4A1	For - 5'-GTTCTACCTGCAAAGGCAATGG-3' Rev - 5'-TGCCCAAAGAACCAGTGGAA-3'	78	60
CYP4A3	For - 5'-TCTCAGGGAGCAAAACACGA-3' Rev - 5'-CAACAGGAGCAAACCATAACCA-3'	134	59

eNOS- endothelial nitric oxide synthase; iNOS- inducible nitric oxide synthase; COX-1- cyclooxygenase 1; COX-2- cyclooxygenase 2; TBXAS1- thromboxane A synthase 1; CYP2J3- cytochrome P450 2J3; CYP4A1- cytochrome P450 4A1; CYP4A3- cytochrome P450 4A3.

Custom-made primers (Primer 3 software) used for gene expression measurements of eNOS and iNOS, COX-1, COX-2, TBXAS1, CYP4A1, CYP4A3 and CYP2J3 and HPRT1 are shown in Table 1.

Reagents

NA, ACh, L-NAME and indomethacin were purchased from Sigma-Aldrich. Ketamine and midazolam were obtained from Pfizer. Streptozotocin was purchased from Sigma-Aldrich. The CO_2 adsorbent Drägersorb 800 Plus was produced by Dräger, Lübeck, Germany. The Krebs-Henseleit solution (composition: 113 mM NaCl, 4.7 mM KCl, 1.2 mM $MgSO_4 \times 7H_2O$, 22 mM $NaHCO_3$, 1.2 mM KH_2PO_4, 11 mM glucose, 2.5 mM $CaCl_2 \times 2H_2O$, 0.026 mM ethylenediaminetetraacetic acid (EDTA); pH 7.4) was prepared from EDTA purchased from Sigma-Aldrich, $CaCl_2 \times 2H_2O$ and $NaHCO_3$ from Merck KGaA, Darmstadt, Germany, with the rest of the chemicals purchased from Kemika, Zagreb, Croatia. MS-PPOH and HET0016 were gifts from John R. Falck, Southwestern Medical Center, Dallas, Texas, U.S. The chemicals used to determine the oxidative stress were thiobarbituric acid (TBA; Sigma-Aldrich, U.S.), trichloroacetic acid (TCA; Panreac, Europe) and 1,1,3,3-tetramethoxypropane (TMP; Sigma-Aldrich).

Statistical analysis

All data are summarized as means ± SEM. Two-way ANOVA tests and Bonferroni post hoc tests were used to test differences in ACh-induced relaxation among groups. Half maximal effective concentration (LogEC50) ACh values were compared by One-Way ANOVA and Tukey post hoc tests. One-Way ANOVA and Tukey post hoc tests were used to measure the difference in body weight, blood glucose, oxidative stress level and gene expression among groups. A probability of $P \leq 0.05$ was considered to be statistically significant. SigmaPlot, version 11.2 (Systat Software, Inc., Chicago, Illinois, U.S.) and GraphPad Prism v5.0 (GraphPad Software, Inc., La Jolla, California, U.S.) were used for statistical analysis and for the graphic presentation of the obtained results.

Table 2. Body weight, blood glucose and oxidative stress level of 12-week-old female rats (n=20 per group)

parameters	CTR	DM	CTR+HBO	DM+HBO
body weight, g	237 ± 6	179 ± 14 *	240 ± 5	209 ± 5 †‡
blood glucose, mmol/L	6.5 ± 0.2	32.5 ± 0.5 *	7.2 ± 0.2	28.7 ± 0.9 †
TBARS, μmol MDA	0.65 ± 0.10	1.03 ± 0.03*	0.94 ± 0.01	1.08 ± 0.04 † §
FRAP, mM Trolox	0.04 ± 0.01	0.04 ± 0.01	0.04 ± 0.01	0.04 ± 0.01

Data are presented as mean ± SEM. n - number of rats; CTR - control; DM - diabetes mellitus; HBO - hyperbaric oxygenation; TBARS - thiobarbituric acid reactive substances; MDA - malondialdehyde; FRAP - ferric reducing ability of plasma.
* P<0.05 CTR vs. DM; † P<0.05 CTR+HBO vs. DM+HBO; ‡ P<0.05 DM vs. DM+HBO; § DM+HBO vs. CTR

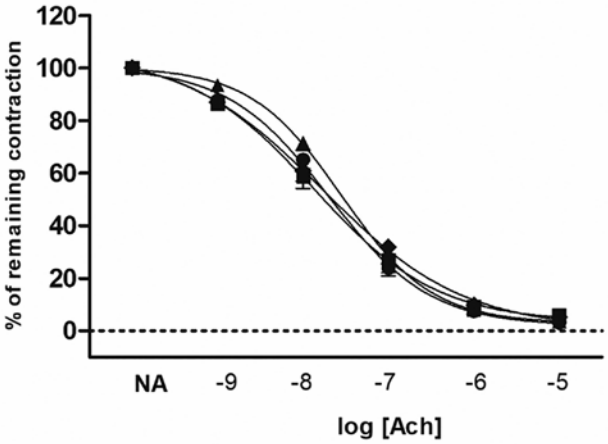
RESULTS

Body weight, blood glucose level and oxidative stress of experimental animals (at the age of 12 weeks)

Body weight, blood glucose level and oxidative stress of all experimental animals are presented in Table 2. Diabetic rats (DM) had lower body weight compared to controls (CTR), which was expected due to untreated DM. Also, diabetic rats that underwent HBO_2 (DM+HBO) treatment had lower body weight compared to healthy controls that underwent HBO_2 (CTR+HBO). Diabetic rats that underwent HBO_2 (DM+HBO) had higher body weight compared to DM rats (Table 2). As expected, blood glucose level was significantly increased in both DM and DM+HBO rats compared to their corresponding controls, which confirmed successful development of Type 1 diabetes model in our experimental protocol (Table 2). DM rats had increased TBARS compared to CTR rats (Table 2). Also, TBARS were significantly increased in DM+HBO rats compared to CTR+HBO (Table 2). Additionally, DM+HBO rats had significantly increased TBARS compared to CTR group of rats. There was no significant difference in ferric reducing ability of plasma assay (FRAP) among experimental groups of rats (Table 2).

Mechanisms of acetylcholine-induced relaxation of isolated rat aortic rings

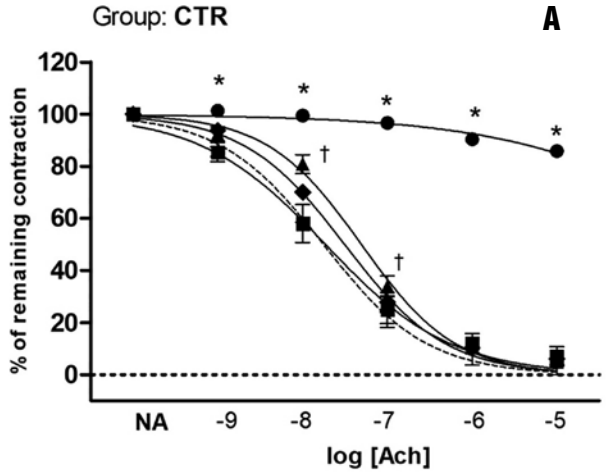
Figure 1 presents the baseline AChIR of isolated rat aortic rings in all experimental groups of SD rats. There were no significant differences in the magnitude of AChIR of isolated rat aortic rings among groups. Also, half maximal effective concentration of ACh (LogEC50) (the sensitivity to ACh) was not significantly different among experimental groups of rats (table within Figure 1).



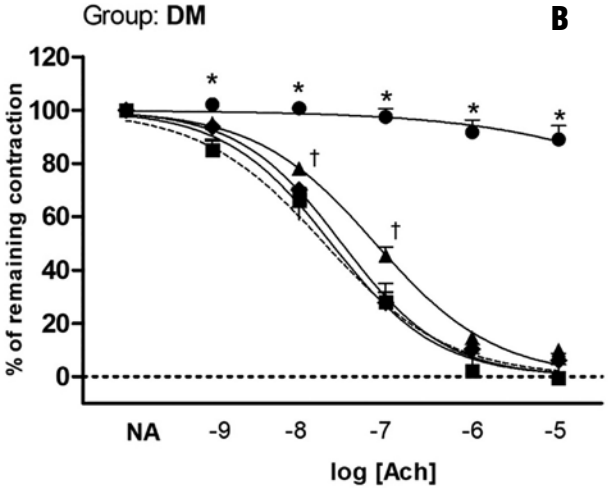
	LogEC50	EC50 (molL-1)
● control (N=20)	-7.776	1.676E-8
■ DM (N=20)	-7.872	1.343E-8
▲ CTR+HBO (N=20)	-7.552	2.807E-8
◆ DM+HBO (N=20)	-7.761	1.735E-8

Figure 1. ACh induced relaxation (AChIR) of isolated rat aortic rings in CTR, DM, CTR+HBO and DM+HBO rats.

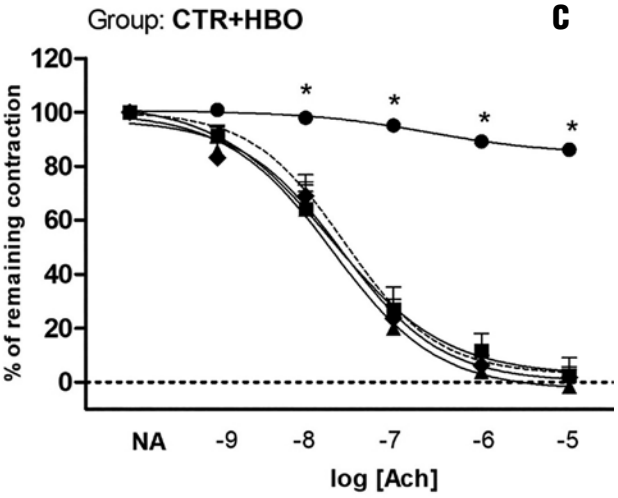
There was no significant difference in AChIR among the experimental groups of rats. There was no difference in the sensitivity to ACh among the groups (table within figure). LogEC50 values (shown in corresponding tables) were compared by one-way ANOVA test.
ACh concentration 10^{-9} to 10^{-5} molL-1. N- number of aortic rings. EC50 (molL-1)- half maximal effective concentration presents concentration of ACh (molL-1) which induces a response halfway between the baseline and maximum.



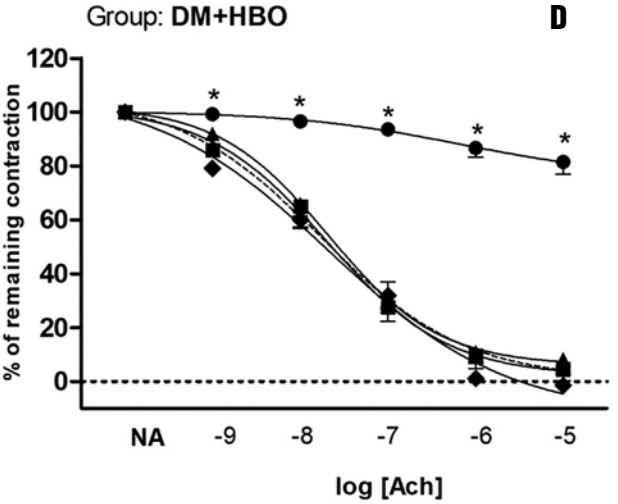
	LogEC50	EC50 (molL-1)
--- baseline (N=20)	-7.776	1.676E-08
● L-NAME (N=17)	-6.303	4.976E-07 ‡
■ INDO (N=16)	-7.950	1.222E-08
▲ MSPPOH (N=11)	-7.355	4.415E-08 §
◆ HET0016 (N=12)	-7.616	2.421E-08



	LogEC50	EC50 (molL-1)
--- baseline (N=20)	-7.872	1.343E-08
● L-NAME (N=16)	-6.552	2.803E-07 ‡
■ INDO (N=17)	-7.542	2.869E-08
▲ MSPPOH (N=11)	-7.248	5.652E-08 §
◆ HET0016 (N=7)	-7.632	2.334E-08



	LogEC50	EC50 (molL-1)
--- baseline (N=20)	-7.552	2.807E-08
● L-NAME (N=16)	- 6.600	2.515E-07 ‡
■ INDO (N=10)	-7.711	1.944E-08
▲ MSPPOH (N=8)	-7.692	2.033E-08
◆ HET0016 (N=9)	-7.638	2.303E-08



	LogEC50	EC50 (molL-1)
--- baseline (N=20)	-7.761	1.735E-08
● L-NAME (N=16)	-6.150	7.086E-07 ‡
■ INDO (N=16)	-7.693	2.029E-08
▲ MSPPOH (N=12)	-7.677	2.106E-08
◆ HET0016 (N=14)	-7.732	1.851E-08

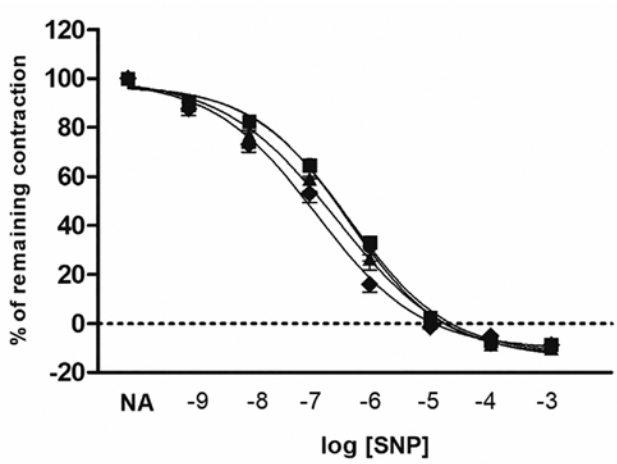
Figure 2. Mechanisms of acetylcholine induced relaxation (AChIR) response of isolated rat aorta rings in CTR (Panel A), DM (Panel B), CTR+HBO (Panel C) and DM+HBO rats (Panel D).

The presence of L-NAME and MS-PPOH significantly reduced AChIR of isolated rat aortic rings in CTR group (Panel A), and DM group of rats (Panel B). Indomethacin and HET0016 administration did not have any significant effect on AChIR in any group, while MS-PPOH administration did not have any significant effect on AChIR in both CTR+HBO (Panel C) and DM+HBO groups (Panel D). Data were compared by two-way ANOVA and Bonferroni post hoc tests. *~ continued on next page*

Potential mechanisms mediating AChIR response of isolated rat aortic rings in experimental groups of rats are presented in Figure 2. In the CTR group the presence of L-NAME and MS-PPOH significantly reduced the AChIR, while INDO (COX-1 and -2 inhibitor) and HET0016 (20-HETE formation inhibitor) administration did not have any significant effect on AChIR in the CTR group of rats (Figure 2, Panel A). Similar results were obtained in the DM group of rats (Figure 2, Panel B). In both CTR and DM groups of rats, analysis of aortic ring sensitivity to ACh demonstrated that the sensitivity to ACh in the presence of L-NAME and in the presence of MSPPOH was significantly decreased compared to the response to ACh alone or in the presence of indomethacin or HET0016 (tables within Panels 2A and 2B). In the CTR+HBO and DM+HBO groups, only the presence of L-NAME, but not MS-PPOH, INDO or HET0016, significantly reduced the AChIR (Figure 2, Panels C and D). Furthermore, in the CTR+HBO and DM+HBO groups, the sensitivity to ACh was significantly lower in the presence of L-NAME compared to the basic response or the response to ACh in the presence of indomethacin, MS-PPOH or HET0016 (Figure 2, tables within Panels 2C and 2D).

Sodium nitroprusside-induced relaxation of isolated rat aortic rings

Figure 3 presents the relaxation of aortic rings in response to SNP (SNPIR), an endothelium-independent NO donor in all experimental groups of SD rats. There were no significant differences in the SNPIR among groups. Also, the sensitivity to SNP was not significantly different between experimental groups of rats (table within Figure 3).



	LogEC50	EC50 (molL-1)
● control (N=9)	-6.357	4.391E-7
■ DM (N=18)	-6.558	2.764E-7
▲ CTR+HBO (N=11)	-6.346	4.505E-7
◆ DM+HBO (N=16)	-6.884	1.307E-7

Figure 3. SNP induced relaxation (SNPIR) of isolated rat aorta rings in CTR, DM, CTR+HBO and DM+HBO rats.

There was no significant difference in SNPIR between the experimental groups of rats. Also, there was no difference in the sensitivity to SNP between experimental groups of rats (table within figure). LogEC50 values (shown in corresponding tables) were compared by one-way ANOVA test. SNP concentration 10^{-9} to 10^{-3} molL-1. N- number of aortic rings. EC50 (molL-1)- half maximal effective concentration presents concentration of SNP (molL-1) which induces a response halfway between the baseline and maximum.

mRNA expression of enzymes catalyzing vasoactive mediators in rat aorta

mRNA expression of iNOS in rat aortic tissue was significantly increased in DM compared to CTR group of rats (Table 3). eNOS mRNA expression was significantly increased in CTR+HBO compared to CTR rats, while TBXAS1 mRNA expression was significantly increased in DM+HBO compared to DM rats (Table 3). COX-1, COX-2, CYP2J3, CYP4A1 and CYP4A3 mRNA expression in thoracic aorta did not significantly differ among the groups (Table 3).

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The sensitivity to ACh in the presence of L-NAME and MS-PPOH was significantly decreased compared to response to ACh alone or in the presence of Indomethacin or HET0016 in both CTR and DM groups of rats (tables within Panel A and Panel B). Sensitivity to ACh in the presence of L-NAME was significantly decreased compared to response to ACh alone or in the presence of other inhibitors in both CTR+HBO and DM+HBO groups of rats (tables within Panel C and Panel D). LogEC50 values were compared by one-way ANOVA followed by Holm-Sidac pairwise multiple comparison. Statistically significant ($p < 0.05$) AChIR in the presence of L-NAME (*) or MS-PPOH (†) compared to baseline ACh response. ‡ $P<0.05$ L-NAME vs. baseline, Indomethacin and MS-PPOH; § MS-PPOH vs. baseline and Indomethacin. N- number of aortic rings. EC50 (molL-1)- half maximal effective concentration presents concentration of ACh (molL-1) which induces a response halfway between the baseline and maximum.

Table 3. Relative mRNA expression of eNOS, iNOS, COX-1, COX-2, TBXAS1, CYP2J3, CYP4A1 and CYP4A3; to HPRT1 in thoracic aorta tissue (n=5 per group)

parameters	CTR	DM	CTR+HBO	DM+HBO
eNOS	0.10 ± 0.01	0.15 ± 0.03	0.16 ± 0.02 §	0.17 ± 0.04
iNOS	1.0E-3 ± 0.3E-3	0.03 ± 0.02 *	2.0E-3 ± 1.0E-3	8.0E-3 ± 2.0E-3
COX-1	0.13 ± 0.01	0.13 ± 0.04	0.14 ± 0.02	0.09 ± 0.02
COX-2	0.16 ± 0.06	0.12 ± 0.08	0.12 ± 0.04	0.09 ± 0.03
TBXAS1	1.12 ± 0.15	1.17 ± 0.11	1.23 ± 0.09	1.67 ± 0.11 ‡
CYP2J3	2.64 ± 0.30	1.93 ± 0.43	2.80 ± 0.23	1.75 ± 0.24
CYP4A1	0.06 ± 0.02	0.05 ± 0.02	0.03 ± 0.01	0.02 ± 0.01
CYP4A3	1.4E-6 ± 2.5E-7	0.8E-6 ± 2.8E-7	1.7E-6 ± 2.5E-7	1.0E-6 ± 1.9E-7

Data are presented as mean ± SEM. n - number of rats; CTR - control; DM - diabetes mellitus; HBO - hyperbaric oxygenation; eNOS - endothelial nitric oxide synthase; iNOS - inducible nitric oxide synthase; COX-1 - cyclooxygenase 1; COX-2 - cyclooxygenase 2; TBXAS1 - thromboxane A synthase 1; CYP2J3 - cytochrome P450 2J3; CYP4A1 - cytochrome P450 4A1; CYP4A3 - cytochrome P450 4A3. * $P < 0.05$ CTR vs. DM; ‡ $P<0.05$ DM vs. DM+HBO; § CTR vs. CTR+HBO

DISCUSSION

Abundant evidence shows that diabetic patients are at high risk for development of CVDs (e.g., coronary heart disease, stroke, peripheral arterial disease, cardiomyopathy, congestive heart failure), and that cardiovascular complications are now the leading causes of diabetes-related morbidity and mortality [30]. It is well established that endothelial dysfunction accompanies DM, and manifests in form of vascular complications that are evident in both macro- and microcirculation [31]. Still, even though vascular alterations are commonly described in patients and experimental animals with diabetes, endothelium-dependent relaxation (assessed by ACh-induced vascular relaxation of isolated rat aortic rings) has been shown to be either unaffected, attenuated or even augmented in experimental diabetic animals [32,33].

Salient finding of the present study is that six weeks of Type 1 DM in female SD rats did not affect the magnitude of the AChIR of isolated aortic rings; however, HBO_2 affected the mechanisms of AChIR. Furthermore, even though DM did not affect the AChIR in female rats, oxidative stress level was significantly increased in both the DM and DM+HBO groups of diabetic rats when compared to controls. These results indicate very early changes in oxidative balance in DM, apparently before measurable functional vascular impairment could be identified. Finally, HBO_2 effects on the mechanisms of AChIR are not related to the level of oxidative stress in any group of female rats.

Increased oxidative stress underlies impaired vascular reactivity in many cardiometabolic diseases, including DM [17,34-37]. However, in the present study increased oxidative stress in the DM group of rats did not affect the mechanisms of ACh-induced vascular relaxation (Table 2, Figure 1). It is known that acute HBO_2 (i.e., single exposures up to 3 ATA) can enhance production of reactive oxygen species (ROS) and increase TBARS [38,39]. Our results show elevated levels of TBARS in both diabetic groups compared to their respective controls, while intermittent HBO_2 did not additionally increase the level of oxidative stress, which is consistent with our previous results [17,25,38].

A number of independent animal and human studies on diabetes reported impaired vascular function in various vascular beds and vessel calibers in terms of enhanced vascular responsiveness to vasoconstrictors and attenuated response to vasodilators [1-4]. For example, a study by Bhwardai, et al. demonstrated that after eight weeks of Type 1 DM, the AChiR of isolated aortic rings was attenuated, accompanied by a decrease in aortic and serum nitrite/nitrate concentrations and impaired aortic endothelial integrity [34]. Furthermore, aortic superoxide levels were increased, together with increased serum lipid peroxidation levels and hyperglycemia [34]. As mentioned, in the present study the mechanisms mediating aortic rings relaxation to ACh have been altered by HBO_2 (in both CTR and DM rats), and the AChIR following HBO_2 was no longer dependent on EETs. Since we did not

observe any significant HBO_2-induced changes in mRNA expression of isozymes that produce EETs, it is possible that HBO_2 affects vascular sensitivity to EETs, rather than affecting its synthesis, which could be concluded from the findings presented in Figure 2 (tables within Panels A and B). Furthermore, the sensitivity to ACh in the presence of L-NAME was also significantly decreased compared to basic response or response to ACh in the presence of indomethacin or MS-PPOH or HET0016 in both CTR+HBO and DM+HBO groups (Figure 2, tables within Panels C and D). However, in the present study, the contribution of 20-HETE or COX-1 and COX-2 metabolites to AChIR was not observed. Potential limitation of the study may be that only mRNA expression of enzymes of interest was performed, and the changes in mRNA do not necessarily provide information on enzyme activities. However, not even enzyme activities must relate to some functional changes, because the quantity of the protein present in the tissue of interest is important, and that may depend on the regulation of expression. Correlations among the mRNA, protein expression, enzyme activity and observed physiological or clinical findings are often weak or not uniform [40-42]. Thus, these kinds of data have to be interpreted cautiously.

Due to untreated disease, the body weight of DM rats was significantly decreased compared to all other groups of rats. Significant increase in blood glucose levels in DM and DM+HBO rats also confirms that DM was properly induced, as expected (Table 2). Although animals exhibited significant symptoms of untreated DM (polydipsia, polyphagia, polyuria), the six-week duration of DM did not affect the magnitude of the AChiR, which was surprising on one hand. However, our findings are partly in accordance with the study of Brown, et al., which demonstrated that DM had little effect on the AChiR of the aortic rings from male and female rats affected with DM for eight weeks and slightly attenuated SNP-induced vasorelaxation, but exhibited some effect on myocyte function, e.g., prolonged duration and maximal velocity of myocardial contraction and relaxation duration in both genders [43]. In the study by Hopfner, et al. the AChIR responses were attenuated in the 14-week group, but not in the two-week group of diabetic rats, while the endothelium-independent (SNP-evoked) responses remained unchanged [44]. This was similar to our results.

Development of changes in vascular reactivity in DM has a temporal manner [44-46]. For example, Pieper, et al. described a three-phase response to AChIR in diabetic male rats. They first saw an enhancement of vascular relaxation at 24 hours after induction of DM; further normalization of vasorelaxation after one and two weeks of DM; and finally, an impaired relaxation in response to ACh eight weeks after induction of DM in the aortic rings model [45]. A temporal manner of the development of vascular impairment could also explain the preserved AChIR in our study at six weeks of DM duration. On the other hand, our experiment was designed to elucidate potential effects of HBO_2 treatment on the mechanisms of AChIR as early as possible, even before manifested vascular complications. Thus, the present results demonstrated that the mechanisms mediating AChIR were affected by HBO_2, although the magnitude of the response (relaxation to ACh) was not affected either by DM or by HBO_2. In such an early phase of DM we failed to demonstrate that the EETs pathway was robustly involved in the vascular relaxation in HBO_2 groups. Some other studies have shown that in female rats in an early DM phase, i.e., at two weeks of DM, there was a modulation of thromboxane A2 production, but no change in the NO system (in its production or in its metabolic pathway, such as phosphodiesterase isoform activities) was observed. At four weeks of DM duration, a reduction in NO activity was superimposed, and the activity of phosphodiesterase was reduced, while the production of vasodilatory prostaglandins was increased, possibly as a compensatory mechanism to maintain normal vascular reactivity [46]. This seems to be specific to female sex [38], since it opposes our findings in male diabetic rats, treated by the same protocol, where all three vasodilator pathways were affected by DM [17].

In the present study, HBO_2 and DM seem to shift the mechanisms of vasorelaxation toward a NO-dependent pathway. The expression profile of enzymes involved in vasoreactivity supports this conclusion, since there was a significant increase in eNOS gene expression in CTR+HBO rats, compared to CTR rats, while iNOS gene expression was significantly increased in DM rats compared to CTR rats. Similar observations were found in the aortas of the Goto-Kakizaki (GK) rat model of genetic Type 2 DM, which exhibited an increased protein expression of eNOS and a decrease in the level of its co-factor tetrahydrobiopterin (BH4). Since GK rats had impaired relaxation to ACh with a significantly enhanced superoxide production and decreased NO bioavailability, the observed increased eNOS protein expression may be of compensatory nature [35]. Our results are in agreement with these observations. However, all changes observed in our study are modest compared to changes in male

DM rats undergoing HBO_2 [17], which might possibly be due to previously observed enhanced ACh-induced vasorelaxation in female compared to male rats (38). In the present study, the relaxation in response to SNP was preserved in all groups (Figure 3), suggesting that a six-week duration of DM and HBO_2 per se do not adversely affect vascular smooth muscle cell responsiveness to NO.

CONCLUSION

The present study suggests that HBO_2 alters the mechanisms of endothelium-dependent vasorelaxation to ACh in female rats very early in the development of Type 1 DM. These effects are slightly different from the previously assessed mechanisms of AChIR in male rats [17]. Since vasorelaxation to endothelium-dependent and -independent stimuli is preserved after six weeks of DM, NO pathway may be upregulated to compensate for decreased sensitivity to both NO and CYP450 vasodilator metabolites of arachidonic acid in DM.

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Conflict of interest statement

The authors declare no conflict of interest exists with this submission.

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RESEARCH ARTICLE

Effects of hyperbaric oxygen therapy on recovery acceleration in Japanese professional or semi-professional rugby players with grade 2 medial collateral ligament injury of the knee: A comparative non-randomized study

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ABSTRACT

Introduction: The effects of hyperbaric oxygen (HBO_2) therapy on sprains, ligament injuries, and muscle strains have been reported in several animal studies. In a dog model of compartment syndrome and in a rat contused skeletal muscle injury model, the significant effects of HBO_2 therapy on the reduction of edema and muscle necrosis have been reported. In basic research HBO_2 therapy stimulated fibroblast activity to improve the healing process. Because of this it expected that HBO_2 therapy might improve focal edema and pain in the acute phase and accelerate the healing of injured tissues in athletes with a medial collateral ligament (MCL) injury of the knee. This study aimed to examine the short-term effects of HBO_2 application subjectively, and the long-term effects of HBO_2 therapy in Japanese professional or semi-professional rugby players with grade 2 MCL injury of the knee.

Methods: Thirty-two professional or semi-professional rugby players with grade 2 MCL injury of the knee were investigated. First, in the HBO_2 group (n=16), HBO_2 therapy was performed during the acute phase. Visual analog scales (VASs) immediately before and after HBO_2 therapy on the same day were compared. Next, we retrospectively evaluated the time to return to play in the HBO_2 (n=16) and non-HBO_2 (n=16) groups.

Results: VAS scores for pain while walking immediately before and after HBO_2 therapy on the same day were 37.4 ± 20.1 (mean ± standard deviation) and 32.4 ± 21.8, respectively ($p<0.001$). The VAS scores for pain while jogging were 50.7 ± 25.6 and 43.9 ± 25.0, respectively ($p<0.001$). The time to return to play was 31.4 ± 12.2 days in the HBO_2 group and 42.1 ± 15.8 days in the non-HBO_2 group, indicating a significant difference between the groups ($p<0.05$).

Conclusion: HBO_2 therapy may reduce pain and accelerate the return to play in athletes with grade 2 MCL injury of the knee in this non-randomized study.

INTRODUCTION

After sustaining injuries during sports, athletes are usually required – and desire – to return to competition rapidly. In particular, high-level athletes are required to return to play as soon as possible. Therefore, safe and effective, multidisciplinary treatments should be established. Athletes prefer such therapies, as they accelerate their return to competition.

Injury to the medial collateral ligament (MCL) of the knee is a frequently encountered sports injury. The incidence rate of MCL injury during sports activity ranges from 0.04 to 3.1 MCL injuries per 1,000 hours of athlete exposures (AEs) [1-3]. Moreover, the incidence rate during rugby competitions is relatively high [1].

As with other soft-tissue injuries, MCL injury undergoes four stages of healing. These include: hemorrhage,

KEYWORDS: hyperbaric oxygen therapy; medial collateral ligament; return to play; pain reduction; recovery acceleration

inflammation, repair, and remodeling [4,5]. The acute inflammatory phase is characterized by edema, pain, and a limited range of motion, which prevents affected individuals from returning to sports activities. A rapid reduction of pain and tissue edema at the injured site during the acute phase would accelerate the healing potential and reduce the time to return to previous levels of competition.

Hyperbaric oxygen (HBO_2) therapy has been noted as effective for wound healing and soft tissue injury, including crush injury and compartment syndrome [6-10]. The effects of HBO_2 therapy on soft tissue injuries during sports activities, including sprains, ligament injuries, contusions, and muscle strains, have been reported by several basic and clinical studies [11].

In the acute phase, HBO_2 therapy improves hypoxic tissue microcirculation following a reduction in edema. In a dog model of compartment syndrome, significant effects of HBO_2 therapy on the reduction of edema and muscle necrosis have been reported [11-13] In animal research HBO_2 therapy stimulated fibroblast activity to improve the healing process [14], and promoted ligament healing and maximum failure load after injury in the remodeling phase in a rat model [15-17]. Clinically, HBO_2 therapy may provide short-term effects such as reducing edema and pain in athletes with acute ankle sprain, as shown in a pilot study [29]. James, et al. first documented the quantitative effectiveness of HBO_2 therapy in sports injuries. In this preliminary report the actual days of unfitness compared to the estimated days assessed by the club physiotherapist resulted in a 70% decrease in injury time for returning to football activities in Scotland [36].

We reasoned therefore that HBO_2 therapy might help improve focal edema and pain in the acute phase and accelerate the healing of injured tissues in athletes with MCL injury of the knee. However, Barata, et al. documented a literature review that demonstrates that although results have proven to be promising in terms of using HBO_2 as a treatment modality in sports-related injuries, these studies have been limited due to the small sample size, lack of blinding, and issues with randomization [22]. As there have been few quantitative evaluations of HBO_2 therapy for MCL injury, HBO_2 effectiveness has not been clarified in detail.

This comparative non-randomized study aimed to evaluate the clinical efficacy of HBO_2 therapy in athletes with grade 2 MCL injury of the knees. The subjects in this study included professional or semi-professional rugby players. The primary outcome was defined as the short-term effects of HBO_2 therapy in the HBO_2 group in the acute phase of injury in terms of subjective VAS evaluation compared immediately before and after HBO_2 therapy. The secondary outcome was defined as the long-term effects of HBO_2 in terms of the time to return to play compared between the HBO_2 and non-HBO_2 groups.

MATERIALS AND METHODS

This study was approved by the institutional review board of Tokyo Medical and Dental University in 2007. Each subject in the HBO_2 group provided written informed consent before participating in the study and starting HBO_2 therapy. This study was undertaken in full accordance with the ethical standards in the Declaration of Helsinki.

Subjects

A total of 32 professional or semi-professional rugby players with grade 2 MCL knee injury that occurred during sports activity and during the rugby season that extended from June to January were investigated in this study. All subjects belonged to the "Top League" Japanese rugby league, which is the top category of the Japanese Rugby Federation.

The diagnosis of grade 2 MCL injury was made via clinical examination by the authors, who were the team medical doctors. Their specialty was orthopedics and sports medicine, and they possessed a keen ability to diagnose injuries accurately.

The grade of MCL injury was judged by manual examination as follows, and any right-left asymmetry was considered a positive finding:

A) **grade 1:** negative instability in the manual valgus stress test at full extension and at 30 degrees of knee flexion, and positive tenderness at the injured MCL site;
B) **grade 2:** negative instability in the manual valgus stress test at full extension, and positive instability in this test at 30 degrees of flexion; and
C) **grade 3:** positive instability in the manual valgus stress test at full extension and at 30 degrees of flexion (Table 1).

Exclusion criteria included a past history of MCL injury and/or other knee joint injuries including anterior cruciate ligament injury or meniscus injury.

From 2007 to 2011 all the patients with grade 2 MCL injury during the acute phase within six days of injury

Table 1. Diagnosis of the grade of MCL injury

	instability by manual valgus test		tenderness
	at full extension	at 30 degrees of flexion	at the injured MCL site
Grade 1	(–)	(–)	(+)
Grade 2	(–)	(+)	(+)
Grade 3	(+)	(+)	(+)

in four teams were referred to our hospital. All the cases were included in this study. All the cases were enrolled, consented, and underwent treatment with HBO_2 therapy (HBO_2 group, n=16). From 2001 to 2006, patients with grade 2 MCL injury were not administered HBO_2 therapy and were determined as the non-HBO_2 group (n=16). The data in the non-HBO_2 group were collected from their team doctors or their trainers.

Hyperbaric oxygen therapy protocol

The HBO_2 chamber in our hospital is a multiplace unit capable of holding 16 patients (NHC-412-A, Nakamura Tekko-Sho Corp., Tokyo, Japan). In this series HBO_2 therapy was performed using 2.8 atmospheres absolute (ATA) (283.6 kPa) for 60 minutes. In the HBO_2 group (n=16), HBO_2 application started as soon as possible, including the same day of injury (Day 0). Each patient received a total of five HBO_2 treatments within 10 days after injury.

Treatment and rehabilitation protocol post injury

All subjects underwent treatment assuming that they would be participating in a competitive match within the same season. The treatment and rehabilitation protocols after injury continued to be non-surgical and included initial rest, cryotherapy, compression, elevation, and restriction of weight bearing in the acute phase within 72 hours [31]. Patients were advised on early rehabilitation, including early range of motion and strengthening exercise of the quadriceps and hamstrings in a standard fashion. Weight bearing was permitted as soon as possible with use of a hinged knee brace when the athlete had moderate or severe pain [31-33]. Finally, after patients' muscle strength, proprioception, agility, and cardiopulmonary function had recovered to levels that were comparable to the contralateral side, the patients were permitted to return to play. The medical staff members for all teams checked this protocol, and confirmed their treatments according to this protocol.

Evaluation

Short-term effects of HBO_2 therapy on the subjective evaluation of pain: VAS evaluation

First, in the HBO_2 group, VAS scores were used to subjectively evaluate pain. These scores were compared immediately before and after HBO_2 therapy on the same day, which means that we assessed differences in the 117-minute treatment. In the VAS evaluation, such question items of *pain at rest*, *pain while walking*, and *pain while jogging* were included. VAS scores consisted of 100 points at full marks, with the worst condition being 100 points and no complaint being 0 points.

Long-term effects of HBO_2 therapy on time to return to play

Second, time to return to play in the HBO_2 (n=16) and non-HBO_2 (n=16) groups was compared. The day of return to play was determined as the day the athlete participated in a competitive match. In the non-HBO_2 group the time to return to play was retrospectively investigated through the team medical records, to which two of the authors had access as medical team doctors. In addition, we analyzed time to return to play regarding teams and field positions in all cases (n=32). We also analyzed time to return to play regarding teams, positions, number of HBO_2 treatments and early or late application of HBO_2 in the HBO_2 group (n=16).

Statistical analysis

In this study data were shown as mean ± SD. Statistical analyses were performed using the Wilcoxon signed rank test for the VAS evaluation, and the Mann-Whitney U test for the evaluation of time to return to play between the HBO_2 and non-HBO_2 groups, and time to return to play regarding positions, length of HBO_2 treatment time and early or late HBO_2 application. The Kruskal-Wallis test was performed for the evaluation of time to return to play among the teams.

All data were analyzed using SPSS version 19.0 (IBM, Armonk, New York, U.S.). The significance level for statistical analysis was set at $p<0.05$.

RESULTS

Demographics of the subjects

HBO_2 group: Mean age of subjects in the HBO_2 group was 27.2 ± 3.3 (range; 22-32) years and all were male. Subjects in the HBO_2 group belonged to these teams: A (six patients); B (four patients); C (three patients); or D (three patients) among 14 teams in the top Japa-

Table 2. Patient distribution

	n	age (years)	height (cm)	body weight (kg)	position		affected side	
					forwards (n)	backs (n)	right (n)	left (n)
HBO_2	16	27.2 ± 3.3 (22-32)	182.l ± 9.3	97.3 ± 14.4	11	5	8	8
Non-HBO_2	16	27.0 ± 2.0 (24-31)	180.5 ± 7.5	89.0 ± 10.9	6	10	8	8

nese rugby league. Rugby positions were distributed as: 11 forwards and five backs, with the right knee affected in 8 patients and the left knee affected in eight patients (Table 2). The mean number of days from injury to the first HBO_2 session was 2.2 ± 1.4 (range; 0-6) days. Five HBO_2 treatments were recommended. However, average number of HBO_2 sessions was 4.6 ± 0.7 (range; 3-5). In total, 73 courses of HBO_2 were performed in 16 patients (three treatments in two patients, four treatments in three patients, five treatments in 11 patients).

Non-HBO_2 group: Mean age was 27.0 ± 2.0 (range; 24-31) years and all were male. Subjects in the non-HBO_2 group belonged to teams A (six patients) or C (10 patients). Rugby positions were distributed as follows: six forwards and 10 backs, with the right knee affected in eight patients and the left knee affected in eight patients (Table 2). Two of the authors were medical doctors from teams A and C, respectively. They managed the medical protocol and records including the recovery process and time to return to play. There were no statistical differences in age, body weight, or height between the HBO_2 and non-HBO_2 groups.

VAS evaluation in the HBO_2 group

We used 58 VAS scores obtained from 13 patients for analysis, excluding three subjects for whom there was insufficient data. The VAS scores regarding pain at rest immediately before and after HBO_2 therapy on the same day were: 18.8 ± 17.7 and 17.3 ± 16.4, respectively ($p=0.11$), for pain while walking; 37.4 ± 20.1 and 32.4 ± 21.8, respectively ($p<0.001$); and for pain while jogging, 50.7 ± 25.6 and 43.9 ± 25.0, respectively ($p<0.001$) (Figure 1).

Time to return to play between the HBO_2 group and the non-HBO_2 group

All subjects were able to participate in a competitive match after injury within the same season. Time to return to play was 31.4 ± 12.2 (range; 10-58) days in the HBO_2 group and 42.1 ± 15.8 (range; 18-71) days in the non-HBO_2 group (Figure 2). There was a significant difference between the two groups ($p<0.05$).

Time to return to play regarding teams, positions, number of HBO_2 treatments, and early or late application of HBO_2

Regarding time to return to play there were no significant differences among the teams, but there were statistical differences between positions (Table 3). Regarding the number of HBO_2 treatments, time to return to play was 21.6 ± 9.6 (range; 10-38) days in the three- or four-treatment HBO_2 group (n=5) and 35.8 ± 9.9 (range; 25-58) days in the five-treatment HBO_2 group (n=11). There was a significant difference between the groups ($p<0.05$). Regarding early or late HBO_2 application, time to return to play was 27.9 ± 9.3 (range; 10-41) days in the early HBO_2 group within two days after injury (n=11) and 39.0 ± 13.1 (range; 23-58) days in the delayed HBO_2 group three to five days after injury (n=5). There were no significant differences between the groups.

DISCUSSION

The healing process of soft tissue injury, which includes MCL injury, is divided into the inflammatory or acute, proliferative, and remodeling phases. In the acute or inflammatory phase, focal injured soft tissue is characterized by tissue hypoxia microvascular dysfunction, tissue ischemia and hypoxia, and edema [5]. HBO_2 therapy can mitigate resolve tissue hypoxia by increasing dissolved oxygen tension. MCL injury in the acute phase is also characterized by edema, pain, and limited range of motion; hence, rapid reduction of pain and tissue edema at the injured site in the acute phase could also accelerate the healing process and return to play.

Skyhar, et al. reported the effects of HBO_2 on tissue edema and necrosis of muscle in the dog compartment model associated with hemorrhagic hypotension. They concluded that those findings might be the results of improvement of oxygenation of hypoxic tissue and reduction of edema, which came from reductions in serum and hematocrit leakage, resorption of extracellular fluid, and improvement in local circulation [11]. They mentioned that the mechanisms – i.e., hyperoxygenation and vasoconstriction [12] – were similar to those of the

FIGURE 1
VAS scores immediately before HBO_2 and after HBO_2

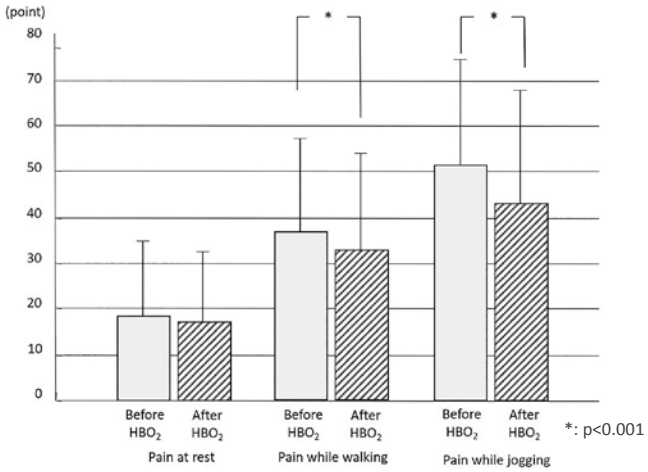
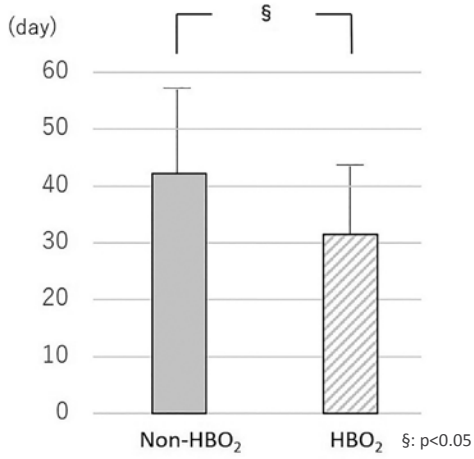


FIGURE 2
Time to return to play in the non-HBO_2 and HBO_2 groups



dog compartment syndrome model in the normotensive state reported by Strauss, et al.

Using a rat contused skeletal muscle injury model Oyaizu, et al. reported that HBO_2 therapy reduced muscle wet weight, and decreased the extracellular space and vascular permeability, which resulted in rapid reduction of edema [30].

Regarding the effects of HBO_2 therapy on ligament healing, the results of several animal research studies have been reported. Horn, et al. used a rat model of surgical MCL laceration with HBO_2 therapy exposure at 2.8 ATA for 1.5 hours a day for five days after surgery [15]. Maximum failure load and stiffness at two, four, six and eight weeks were analyzed. The maximum failure load and stiffness at four weeks in the HBO_2 group were statistically greater than in the control group. Moreover, the HBO_2 group reached normal levels at four weeks. However, the HBO_2 group at six weeks was not statistically different from the control group, which suggested that HBO_2 therapy accelerated the return to normal ligament level.

Mashitori, et al. created a 2-mm segment of MCL in a rat model and applied HBO_2 therapy at 2.5 ATA for two hours a day for five days. Maximum failure load and type I procollagen gene expression at 14 days in the HBO_2 groups statistically increased in conjunction with HBO_2 application[16]. Ishi, et al. examined the effects of three different HBO_2 exposures on the healing of rat patellar ligament injury: HBO_2 exposures included 1.5 ATA for 30 minutes, 2.0 ATA for 30 minutes, and 2.0 ATA for 60 minutes once a day and for 10 sessions. After two weeks, HBO_2 therapy at 2.0 ATA for 60 minutes was

Table 3. Time to return to play regarding the teams and positions

	HBO_2				non-HBO_2			
Team	Number	Forwards (n)	Backs (n)	subtotal	Number	Forwards (n)	Backs (n)	subtotal
A	6	27.3±11.0 (4)	43.5±5.5 (2)	32.5±12.0 (6)	6	52.0±19.0 (2)	40.3±11.3 (4)	44.2±15.4 (6)
B	4	25.5±2.5 (2)	26.5±3.5 (2)	26.0±3.1 (4)				
C	3	31.5±6.5 (2)	58 (1)	40.3±13.6 (3)	10	42.5±14.5 (4)	39.7±15.3 (6)	40.8±15.1 (10)
D	3	27.3±11.0 (3)		27.3±11.0 (3)				
Total	16	27.6±26.6 (11)*	41.2±12.0 (5)*	31.4±12.2 (16)	16	45.7±16.7 (6)	39.9±13.9 (10)	42.1±15.8 (16)

statisitical difference between forwards and backs *: p<0.05 (average ± SD days)

the most effective, resulting in enhanced extracellular matrix deposition as measured by collagen synthesis [17]. Possible mechanisms of action of HBO_2 on ligament injury include reduction of edema and swelling, and promotion of fibroblast proliferation in the scar tissue to produce more type I procollagen mRNA[16].

Clinical reports of the time loss due to MCL injury had been variously documented. The time loss in grades 2 and 3 MCL injury in the U.S. Military Academy study was reported as 29 days [2], and the Union of European Football Association injury study reported 23 ± 23 days of layoff time in 346 MCL injuries [34]. Derscheid, et al. reported a mean return to football within 20 days in patients with grades 1 or 2 MCL injuries who were treated non-operatively [35]. Regarding rugby, especially in high-level rugby players at a professional or semi-professional level, Dallalana, et al. reported knee injuries in the English professional rugby union, and documented a time loss of 41 days in grade 2 MCL injury [1].

However, clinical data is scarce regarding the short- and long-term effects of HBO_2 therapy in patients with MCL injury. Moreover, little is known regarding its effect in accelerating recovery time. Only Soolsma reported the effects of HBO_2 therapy on functional recovery during the fourth, fifth and sixth week after injury using a double-blind controlled study. However, this study has not been published as an original article but only as a university report [28].

This study is the first clinical report regarding the short-term effects of HBO_2 therapy on subjective symptoms and the long-term effect of HBO_2 therapy on return to play, comparing an HBO_2 group with a non-HBO_2 group. Time to return to play is influenced by many factors, including the athletic event; field position; circumstances of schedule; other conventional treatment protocols, including RICE (rest, ice, compression and elevation) treatment at the acute phase; and post-injury rehabilitation protocol. In this study, in order to minimize the effect of subject bias, all subjects were professional or semi-professional rugby players who belonged to the same top category of the Japanese Rugby Federation.

In this study, the VAS scores regarding pain while walking and jogging were significantly reduced, which indicated an increase in the short-term effect of HBO_2 therapy. The VAS scores for pain at rest were not significantly different between immediately before and after HBO_2 therapy, but the VAS scores while walking and jogging were significantly different. Walking and bending the knee joint increased the tissue pressure, and this increase exacerbated the knee pain around the MCL. HBO_2 application helps reduce edema and tissue pressure and would have effects on reduction of VAS scores during walking and jogging.

The time to return to play in the non-HBO_2 group was 42.1 days, which is consistent with the Dallalana, et al. report on conventional treatment in professional rugby players. Thus, it was considered that the control group of non-HBO_2 therapy in this study was suitable, and the time to return to play of 31.4 days in the HBO_2 group was judged as significantly valuable data in regard to the long-term effects of HBO_2 therapy on the acceleration of recovery. Regarding number of HBO_2 treatments, there was a significant difference between the three- or four-treatment HBO_2 group and the five-treatment HBO_2 group. We speculated that the subjects in the five-treatment HBO_2 group might include cases of greater severity.

LIMITATIONS

We recognize several limitations of this study. First, this was not a prospective comparative study, and it is not possible to exclude that factors related to the intervention, including a possible placebo effect, may have confounded the results. The number of subjects was small, and the injury periods of the HBO_2 and non-HBO_2 groups were different. The subjects in this study belonged to the top-level category; however, the HBO_2 group included four teams, whereas the non-HBO_2 group included only two teams. The results showed the wide range of recovery time, which might include mild and severe cases of grade 2 MCL injury for the subjects in this study. In addition, it will be necessary to examine differences in the effects of HBO_2 therapy on injured tissue compared to non-injured healthy tissue, as well as conventional therapies such as RICE treatment and/or use of orthotics.

The VAS evaluations immediately before and after HBO_2 therapy had the possibility to show only the effects of the 117-minute rest. The VAS scores of the patients who had not received HBO_2 and simply had 117 minutes of rest would be more appropriate as a control. In addition, the VAS evaluation in the non-HBO_2 limb would be performed hopefully for comparing the effects of HBO_2 on the healthy limb and injured limb in the future.

HBO_2 can have positive effects on MCL injuries. However, practitioners should be cautious in using HBO_2 therapy for off-label sports medicine injuries.

CONCLUSION

We examined the effects of HBO_2 therapy on professional or semi-professional Japanese rugby players with grade 2 MCL injury that occurred during sports activities. HBO_2 therapy could have a short-term effect on pain reduction during the acute phase, and a long-term effect on acceleration of recovery with a decreased time to return to play.

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RESEARCH ARTICLE

Trends and characteristics of cases when serial carboxyhemoglobins are obtained

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ABSTRACT

Background: Carboxyhemoglobin (COHb) levels are obtained when there is suspicion for carbon monoxide (CO) exposure. Serial COHb levels are sometimes obtained despite the well-established half-life of COHb with oxygen supplementation. We sought to evaluate the trends and characteristics associated with obtaining serial carboxyhemoglobin levels.

Methods: A retrospective review was performed at an academic medical center for all inpatient and emergency department cases with either single COHb or serial COHb levels from 1 April 2010 through 31 March 2015. Data collected included age, gender, pregnancy status, smoking history, encounter month, admission status, oxygen administration, fire or burn history, vital signs, presenting symptoms, hyperbaric oxygen (HBO_2) therapy use, initial pH, troponin, lactate, and COHb levels. The time and change in values between serial levels were also obtained.

Results: 624 cases were identified, with 106 (17%) having multiple carboxyhemoglobin levels. A mean of 2.6 (range 2 - 9) serial COHb levels were obtained. The average initial COHb was 8.9%. Subsequent serial levels were obtained on average at 353, 663 and 1,095 minutes and averaged 2.8%, 1.8% and 1.1% respectively. Serial COHb levels were obtained more commonly in burn patients, those admitted to the ICU and those who had HBO2 therapy. Four patients had an increase in COHb level on serial testing. The largest increase of these was from 2.0% to 3.9%.

Conclusion: Serial COHb levels were not infrequent in this study. No clinically significant increase in COHb was identified by serial testing. Further studies should examine the clinical utility of such practices.

INTRODUCTION

Carbon monoxide (CO) exposures are frequently seen in the emergency department [1]. CO poisoning is among the most common accidental poisonings in the United States, accounting for up to 50,000 emergency department visits and 1,300 deaths per year [1,2]. CO is not detectable by any human sense, and symptoms of CO exposures are vague and non-specific. These include headache, nausea and vomiting in more mild cases, with syncope, ataxia, chest pain, visual disturbances, and focal neurologic deficits seen in more severe cases [3]. At times presenting symptoms can be severe, including coma or cardiopulmonary arrest [3].

Diagnosis of carbon monoxide poisoning is clinical, but acute exposure to carbon monoxide can be confirmed by demonstrating an elevated blood carboxyhemoglobin (COHb). COHb is formed when CO binds to hemoglobin, which it does so with an affinity of up to 210-250 times greater than oxygen [4].

The preferred method of detecting COHb is by testing arterial or venous blood samples with a laboratory CO-oximeter. Standard pulse oximetry cannot accurately detect COHb and may provide false reassurance to providers by measuring falsely elevated oxyhemoglobin saturations in patients with true carbon monoxide poisoning

KEYWORDS: carbon monoxide; carboxyhemoglobin; hyperbaric oxygen therapy; research

Table 1: Comparison of multiple COHgb vs. single COHgb cases.

	multiple COHgb (n=106)	single COHgb (n=515)	p-value
average age (range)	49.8 (9-88)	47 (1-98)	.3636
percent male (n)	63.2 (67)	62.0 (321)	.3948
percent smokers (n)	46.2 (49)	40.5 (210)	.8346
mean initial COHgb (range)	9.0 (0.2-45.2)	3.0 (0-40.6)	.3883
percent burn Injury (n)	64.2 (68)	50.0 (259)	.0103
percent admitted (n)	86.8 (92)	75.3 (390)	.0001
percent ICU admit (n)	64.2 (68)	35.1 (182)	.0001
percent receiving HBO_2 therapy (n)	14 (15)	3.5 (18)	.0001
death (n)	7.5 (8)	5.4 (28)	.3675

[5]. New multiwave pulse CO-oximetry tools designed to detect carboxyhemoglobin are available. Some studies have questioned their accuracy and there is concern they may overestimate carboxyhemoglobin levels when compared to conventional laboratory CO-oximetry [6].

COHb is a very stable complex. In patients breathing room air COHb has been demonstrated to have a half-life of approximately four to six hours [7]. However, this can be decreased to approximately 80 minutes in response to breathing 100% normobaric oxygen or approximately 20 minutes if receiving hyperbaric oxygen [7,8].

Despite the well-established kinetics of COHb elimination, serial COHb levels are often obtained in clinical practice. We sought to evaluate the results and clinical characteristics of cases where serial COHb levels were obtained.

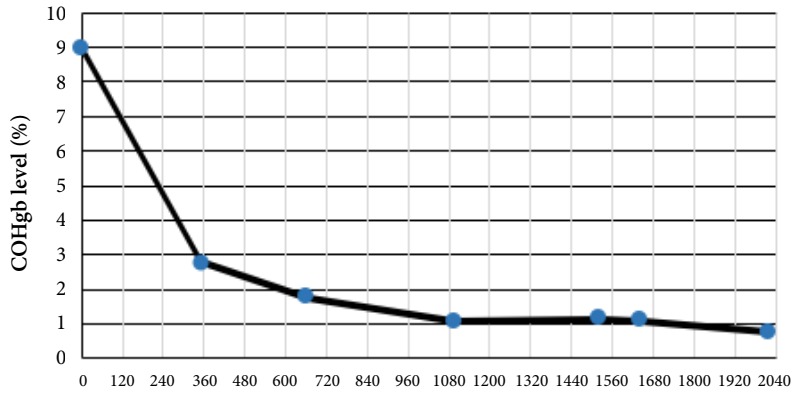
METHODS

This study was an IRB-approved retrospective chart review of the emergency department and inpatient charts of a 650-bed quaternary care level 1 trauma academic medical center with a burn unit and an emergent hyperbaric oxygen therapy unit in Kansas City, Kansas. In this institution COHb levels are ordered and resulted as an individual lab and not as part of a blood gas panel. Patients being evaluated for acute CO exposure with at least one carboxyhemoglobin level, either venous or arterial, obtained during the time span of 1 April 2010 through 31 March 2015 were included in the study. Patients who had carboxyhemoglobin levels drawn and who were being evaluated for transplantation or for pulmonary function testing were excluded from the study. Data was abstracted by the authors. Inter-rater reliability was assured through training and evaluation of Kappa scores which after two training periods was 0.9 among all reviewers. Data was collected via a standardized data collection tool. Collected data included age, gender, pregnancy status, smoking history, month of encounter, admission level of care, administration of oxygen, history of fire or burn, vital signs, presenting symptoms, use of hyperbaric oxygen (HBO_2) therapy, initial pH, and troponin, lactate and carboxyhemoglobin levels. Cases with serial COHb levels were further identified; the timing of each level was also obtained and delta-times were calculated. For this study a COHb level of >2% was considered abnormal for non-smokers and >5% for smokers [9]. Statistical calculations were performed using Microsoft Excel (Redmond, Washington, U.S.).

RESULTS

The search identified 2,213 cases. Of this group 624 cases had an associated ED or inpatient encounter where there was a concern for acute CO exposure. The other cases were transplantation or pulmonary function testing patients and were excluded, as they were not being evaluated for possible carbon monoxide exposures. A total of 106 (17%) of cases who met inclusion criteria had multiple carboxyhemoglobin levels obtained during their encounter. Table 1 compares the characteristics of the cases with multiple COHb results versus those with a single COHb result. The mean number of COHb levels obtained was 2.6 (range 2 - 9), with a total of 167 COHb levels obtained after the initial COHb result. Figure 1 demonstrates the

Figure 1: Average COHgb levels over time



trend of serial COHb levels over time. The average initial level was 9.0% (SD 10.0). Subsequent levels averaged 2.8% (SD 3.3) at 353 minutes; 1.8% (SD 1.8) at 663 minutes; 1.1% (SD 0.94) at 1,095 minutes; 1.1% (SD 0.71) at 1,525 minutes; 1.1% (SD 0.86) at 1,644 minutes; and 0.75% (SD 0.05) at 2,023 minutes. The longest interval time between initial and final serial COHb was 3,807 minutes (2.6 days) in one case where a total of four levels were obtained.

Four patients were identified as having a change in carboxyhemoglobin level from normal (defined as <2% by the institution lab) to abnormal on serial levels. The largest interval increase was from 1.9% to a level of 3.9%. All four of these patients were current smokers: Three were presenting for burn injuries and one was presenting with altered mental status. None of their carboxyhemoglobin levels exceeded 4% at any time, and none of the four died. There were 36 deaths (28 in the single COHb group and eight in the serial COHb group) in this study but no difference in mortality rates between the two groups. HBO_2 therapy was utilized in 32 cases (5%), including 15 times in the serial COHb group. Of these 15, 66% (n=10) had COHb levels checked after HBO_2, which resulted in 1.3% (range 0.2% -3.5%).

DISCUSSION

Exposure to carbon monoxide is among the most commonly encountered poisonings [10]. The measurement of COHb remains the gold standard test to identify acute CO exposures [11]. Despite its widespread use the actual prognostic value of any particular COHb level is unclear [12]. It is even less clear if there is any clinical value in obtaining serial COHb levels. The elimination half-life of COHb under various conditions has been well studied and is predictable to within a narrow time range [8]. Thus, barring a concern for ongoing exposure to CO, repeating COHb levels in the acute care setting would appear to have little clinical value.

This study demonstrated that obtaining serial COHb levels was not rare, occurring in 17% of possible CO exposure cases. The practice of obtaining serial COHb levels was more commonly seen in burn victims and those admitted both to the hospital and the ICU. Not surprisingly, the results of the serial COHb levels demonstrated a consistent decline. We could not identify any case where a repeat COHb testing resulted in identifying a significant COHb increase. In no cases where initial COHb was elevated did a subsequent COHb result in an increased level. Ironically, patients with serial COHb levels were also more likely to receive HBO_2 even though HBO_2 therapy would reduce the elimination half-life of COHb to approximately 20 minutes. Considering that typical HBO_2 treatments are longer than two hours, post-HBO_2 COHb levels would never be expected to be abnormal. Not surprisingly, all post-HBO_2 COHb measurements in this study were normal.

This study was not designed to assess the economic impact of serial COHb testing. The cost of performing COHb testing and the charge to patients will vary between institutions though the Centers for Medicare and Medicaid report a reimbursement of rate of $14.07 per test [13]. Similarly, this study was not designed to detect the impact of serial COHb testing on length of stay.

LIMITATIONS

This study has several limitations. It is a retrospective study and is subject to the possibility of incomplete charting. In addition, it was performed at a single center, and external validity may be limited. Only COHb levels obtained at our institution were recorded. We did not record if a patient had a COHb level drawn at an outside facility prior to transfer. Finally, we could not rule out that some patients may have continued to smoke tobacco while admitted, thus elevating their COHb levels.

CONCLUSION

Serial COHb levels were not infrequent in this study. No clinically significant increase in COHb was identified by serial testing. Serial COHb tests were more likely to be ordered on patients with burns and those admitted to the hospital and ICU. Further studies should examine the clinical utility of such practices.

Conflict of interest statement
The authors declare no conflict of interest exists with this submission.

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RESEARCH ARTICLE

Different treatment protocols for moderate idiopathic sudden sensorineural hearing loss

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ABSTRACT

Treatment of idiopathic sensorineural hearing loss (ISSNHL) is problematic due to the unclear etiology of the illness. Corticosteroid is recommended by some papers, and hyperbaric oxygen (HBO_2) by others. Recently HBO_2 has been shown to be an important therapy for ISSNHL, with an increasing number of studies demonstrating its beneficial results. Recovery from ISSNHL depends on the interval period between onset and treatment, hearing loss severity and audiogram type used to determine damage. Treatment of ISSNHL requires a detailed analysis.

In this retrospective study we reviewed data from 56 patients with moderate ISSNHL. These patients were divided into three groups based on different treatments: corticosteroid group; corticosteroid + HBO_2 (combination)group; and HBO_2-only group. Additionally, all patients received intravenous vasodilator treatment. Hearing levels before and after treatment were compared. All three groups had a similar recovery rate, with an effective rate of more than 50%, and a hearing gain average of 17.38 decibels (dB). HBO_2 treatment got a higher recovery rate. The combination therapy, which included corticosteroid and HBO_2, did not elevate the recovery rate.

INTRODUCTION

Idiopathic sudden sensorineural hearing loss (ISSNHL) is experienced by patients with a hearing decrease of more than 30 decibels (dB) over at least three consecutive frequencies in a period of three days. These sudden hearing changes present a problem often seen in the ENT clinic. Application of corticosteroid, either by systemic intake or intratympanic injection, is recommended for treatment of ISSNHL by some studies and guidelines [1]. Hyperbaric oxygen (HBO_2) therapy, however, is secondary to corticosteroid as a salvage treatment [1-3].

As part of initial treatment, the effect of adjuvant HBO_2 therapy has shown conflicting results in recent studies. When comparing pharmacotherapy only and pharmacotherapy with HBO_2 in the treatment of ISSNHL, some studies showed similar effects [4-7], while others demonstrated favorable effectiveness of HBO_2 and a combination of HBO_2 with corticosteroid, especially for severe to profound hearing loss [8-11].

Given the fact that different hearing loss severities (mild to profound) and audiogram type (low frequency, flat and high frequency) had distinct recoveries, and interval time from onset to treatment greatly influenced the results, treatment of ISSNHL has been problematic. For example, severe and profound hearing loss was sensitive to HBO_2 [8, 9], low frequencies showed better improvement without any treatment [5, 12], and corticosteroids were not effective for ISSNHL at lower frequencies [13].

Until now, the treatment of moderate ISSNHL has not been well analyzed. This retrospective study aims to compare the effectiveness of different treatments, and to demonstrate the effectiveness of HBO_2 when accompanied with a vasodilator.

MATERIALS AND METHODS

Patients

Data for patients treated at our hospitals between January 2010 to June 2018 were reviewed. Only those matching the ISSNHL definition, with unilateral moderate hearing loss (46-75 dB decrease), and less than 14 days' onset were included [14]. Exclusion criteria were as follows:

KEYWORDS: sensorineural hearing loss; corticosteroids; hyperbaric oxygen therapy

- age younger than 18 years;
- history of fluctuant or repeated hearing loss;
- previous ipsilateral or contralateral hearing loss;
- bilateral hearing loss; intracranial neoplasms and presentation with acute neurological symptoms;
- interval time longer than 14 days.

The interval time was defined as the period between disease onset and treatment: If the patient accepted treatment on the same day of onset, the interval time was described as 0 days in this study.

All patients underwent a detailed history and physical examination. Hearing level for each subject was examined with pure tone audiogram (PTA) and acoustic impedance. Blood biochemistry and complete blood count were tested. Temporal computed tomography (CT) and magnetic resonance imaging (MRI) were performed for all patients.

Treatment and hearing evaluation

Patients were divided into three groups according to treatment patterns:

- corticosteroid group;
- corticosteroid + HBO_2 (combination) group; and
- HBO_2-only group.

All patients accepted concurrent intravenous administration of vasodilator with an injection of extract of ginkgo biloba leaves (Dr. Willmar Schwabe GmbH & Co. KG, Germany). Thrombolytics and/or mecobalamin were used in some patients as an additional treatment to the ginkgo. Choice of treatment was based on the patient's condition, contraindication(s), and accessibility of the HBO_2 unit. If the HBO_2 treatment lasted fewer than five days or corticosteroid fewer than three days, the patient was not considered to have accepted this treatment.

The corticosteroid treatment was dexamethasone, administered intravenously: 5-10 mg according to patient weight over seven days. If the patient demonstrated no recovery, tapering with oral prednisone was conducted over the next week. HBO_2 was started within three days of admission and performed as the standard protocol for five to 20 days. The inpatient treatment was generally conducted over a two-week period, and the hearing test was performed every week or whenever a patient indicated a significant recovery. Hearing improvement level was classified as:

- complete recovery (final hearing level ≤25dB);
- partial recovery (>15 dB hearing gain and final hearing level 26-45 dB);
- slight improvement (>15 dB hearing gain and final hearing level 46-75 dB); and
- no improvement (<15 dB hearing gain) according to a modified Siegel's grade [14].

The patients were discharged home after seven to 14 days of treatment. Some patients with partial recovery or no improvement accepted HBO_2 treatment up to 20 days. Follow-up lasted for six months.

Statistical analysis

Hearing levels before and after treatment at decreased frequencies were recorded. Complete recovery, partial recovery and slight recovery were regarded as effective treatment. IBM SPSS Statistics Version 19 (IBM Corp., Armonk, New York, U.S.) was used for the statistical analysis. Demographic data and hearing outcomes were expressed as mean ± standard deviation (SD) or n%. Analysis of variance (ANOVA) was performed for group comparisons. Results were evaluated using a confidence interval of 95%, and a two-sided $p < 0.05$ was considered significant.

RESULTS

Fifty-six patients matched the inclusion criteria. The corticosteroid group included 16 patients, the combination groups comprised 32 patients, and the HBO2 group had only eight patients. The age, gender, interval time and course of treatment showed no significant differences among the three groups (Table 1).

All groups showed significant recovery after treatment. The effective rate was ≥50% (Table 2). The average hearing improvement was 17.38 dB for all patients, while when it came to patients with complete and partial recovery, the number increased to 31.45 dB. The combination group showed better hearing gain (33.88 dB), and the HBO_2 group showed the best recovery rate (62.5%), but there was no significant difference among the three groups ($p>0.05$). Among the three groups no patients showed only a slight recovery. The combination group and corticosteroid group included more patients with a flat-type audiogram (27/32 and 11/16 respectively), while the HBO_2 group had only two in eight patients. These patients achieved a recovery rate of less than 50% (17/40). For the patients with high-frequency decreases, the corticosteroid group included five cases and obtained preferable result with a recovery rate of 80% (4/5), while the other two groups included two and three cases respectively with a lower recovery rate (≤50%). As to the lower-frequency hearing loss, all six patients in the

Table 1: Demography of the ISSNHL patients in three groups

groups	number	age (years)	gender	interval days	treatment days
corticosteroid	16	48.31±16.47	M7 F9	4.31±3.05	9.25±2.65
combination	32	48.06±14.05	M18 F14	4.44±3.78	10.44±3.13
HBO_2	8	51.13±17.10	M4 F4	4.38±2.67	10.13±3.94

Table 2: Treatment results

group	complete recovery	partial recovery	no improvement	effective rate	averaged hearing gain (dB)	effective hearing gain
corticosteroid	5	4	7	56.25%	17.22±15.72	29.65±7.22
combination	8	8	16	50.00%	17.36±19.99	33.88±11.04
HBO_2	2	3	3	62.50%	17.76±13.97	26.91±7.69

combination and HBO_2 groups showed recovery, including complete recovery in two cases and partial recovery in four cases.

DISCUSSION

The current retrospective study showed similar recovery rates in moderate ISSNHL between systemic corticosteroid + vasodilator treatment; corticosteroid + HBO_2 + vasodilator treatment; and HBO_2 + vasodilator treatment. HBO_2 with vasodilator was competent to improve hearing, while HBO_2 with corticosteroid and vasodilator did not promote recovery rate any further.

Most of the literature compared treatment effect without classification of the hearing level severity and audiogram type, which varied significantly and thus affected recovery rate extensively [6, 8, 11, 12]. In addition, results were also influenced by the interval time from disease onset to treatment. It is well known that early treatment often leads to better outcomes, and 10 to 14 days after onset was considered the dividing line [6, 10, 14]. In this paper, only patients with initial ipsilateral ISSNHL and history of fewer than 14 days were admitted. It helps to compare the effect of different treatments, avoiding the influence of delayed treatment and other diseases. In some papers, the HBO_2 or corticosteroid treatments lasted for 10 days or more. A patient with good recovery generally has obvious improvement at about seven days after treatment is begun, so we included patients who underwent treatment longer than five days.

For the uncertain etiology of ISSNHL, various therapies are currently used to improve hearing. In general clinical practice, vasodilator, thrombolytics, vasoactive substances and vitamins also serve as conventional treatments [1, 13, 15], but only corticosteroids and HBO_2 are considered useful. Corticosteroids are accepted by most doctors and guidelines, with an anti-edematous effect as the underlying mechanism. HBO_2 has been used for ISSNHL treatment since the 1960s. It helps to improve tissue hypoxia, and more recently it has been used as the initial treatment for ISSNHL [6-8]. Both treatment methods with coricosteroids or HBO_2 respectively have favorable results, but when used together, there is debate. Toroslu, et al. found addition of HBO_2 to corticosteroid did not improve the average PTA values [6-8]. Eryigit and others showed the overall enhancement of hearing recovery rate in patients treated with PTA and systemic corticosteroids versus those treated with systemic corticosteroids alone [10, 16]. In our study, all patients accepted the vasodilator injection as the basic treatment. Three groups presented a similar recovery rate, and the addition of HBO_2 to corticosteroid showed no special benefit for moderate hearing decreases. The HBO_2 group had a higher recovery rate, and the combination group had the lowest recovery, in line with a previous report [5]. Of course, there is no obvious statistical difference between these groups, but this phenomenon may cause some confusion. We do not know why adding HBO_2 has a lower recovery rate in Kratochvílovà's study [5], while in

this paper there is more flat-type hearing loss in the combination group, which presented lower recovery (42.50% or 17/40) and may influence the final results. Currently our study demonstrates corticosteroid has the same effect as HBO_2 for moderate ISSNHL. The accepted spontaneous recovery rate of ISSNHL is 35%-39% [12]; additional treatment can improve it approximately 10% or more [5-7, 14, 16]. Actually, since we do not know which treatment is helpful, more precise and randomized controlled studies are needed.

The overall efficacy was 53.57% (30/56) in the present study, and the hearing regain was the same as others, from 18.8 dB to 19.3 dB [6,10]. In published articles, treatment with corticosteroid – whether HBO_2 or a combination – showed the recovery rates ranged from 32.5% to 96% [5-7, 14, 16, 17], depending on hearing loss severity or type. For instance, in Cekin's study, the combination of HBO_2 and corticosteroid had the same effect as the corticosteroid only: 71.3% in the control group and 78.95% in the study group. The underlying reason may be that 34 of 36 patients treated within three days of the problem onset [4].

One strange problem emerged in the present study: No patient made a just slight recovery (>15 dB hearing gain and final hearing level 46-75 dB). That means moderate hearing loss has two kinds of results in this study: better hearing or no improvement. But normally, hearing level after treatment should show a slight improvement. We postulate that the patient number was not large enough to contain all types of recovery. Cheng's study showed the same result. Moderate ISSNHL (46-75 dB) had higher recovery with initial concurrent intravenous and intratympanic corticosteroid treatment (96% or 23/24), though the overall rate was only 50.91% (56/110) [14].

CONCLUSION

The current study proved that HBO_2 has the same effect as corticosteroid treatment for moderate ISSNHL within the first 14 days. Combination treatment with HBO_2 and corticosteroid did not achieve a better outcome. Early diagnosis and treatment for ISSNHL was beneficial for recovery regardless of the therapeutic methods. Whether HBO_2 could replace corticosteroid for moderate ISSNHL still needs a larger-sized sample and randomized study.

Conflict of interest statement
The authors have declared that no conflict of interest exists with this submission.

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RESEARCH ARTICLE

Hyperbaric oxygen therapy in treatment of sudden sensorineural hearing loss: finding for the maximal therapeutic benefit of different applied pressures

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ABSTRACT

We compared the efficacy of hyperbaric oxygen (HBO_2) therapy used in the treatment of sudden sensorineural hearing loss (SSNHL) as a supplementary therapy to the first-line medical treatment according to the different applied pressures used in HBO_2 treatment while maintaining the same number of sessions, periodicity and exposure times.

We evaluated data from 115 patients suffering from SSNHL within seven days of hearing loss: 35 patients received the standard treatment protocol (control group), and 80 individuals were treated with additional application of HBO_2 therapy pressured to 2.0 ATA (H2.0; n=49) or 2.5 ATA (H2.5; n=31), respectively. Treatment success was assessed using pre- and post-treatment audiograms.

We found significant differences in both HBO_2 groups compared to the control group. In low frequencies the most significant differences can be seen in both H2.0 and H2.5. In spoken speech frequencies only the H2.0 group was statistically significant. In high frequencies the therapeutic benefits were the lowest.

Furthermore, we found a notable difference in the therapeutic effect of HBO_2 therapy according to the different applied pressure. At low frequencies, the use of 2.5 ATA pressure was more efficient. However, in the higher frequency ranges, the better hearing gains were obtained at the 2.0 ATA pressure.

Our results support the possibility of optimizing treatments individually, depending on the type and frequency range of hearing impairment (shape of the audiogram) in favor of using the 2.0 ATA. This is important in terms of an individual approach to each patient as well as to minimize the burden of a patient in order to obtain the maximum therapeutic effect.

INTRODUCTION

According to the latest data from the World Health Organization [1] about 466 million people worldwide suffer from disabling hearing loss, and 34 million of them are children. It is estimated that by 2050 more than 900 million people will suffer from disabling hearing loss.

Sudden sensorineural hearing loss (SSNHL) is acute hearing loss that develops within 72 hours. The overall incidence of SSNHL ranges from five to 20 per 100,000 subjects a year, both male and female, typically between 30 and 60 years of age [2]. SSNHL is thought to be the clinical manifestation of various pathologic conditions, and is not a simple disease entity. It is defined as 30 dB or more of sensorineural hearing loss over at least three consecutive frequencies within three days [3-5]. The etiology for sudden sensorineural hearing loss is defined in only 10% of cases, whereas the rest are labeled as idiopathic (ISSNHL) [6,5].

Although the pathogenesis of ISSNHL remains largely unknown, there are several hypotheses that may explain the origin of this disease. The most commonly discussed hypotheses include the following: decreased cochlear blood flow with cochlear hypoxia; viral infection; intralabyrinthine membrane rupture; and immune-mediated inner ear disease [7,8]. Because of the multifactorial etiopathology of ISSNHL, many different regimens have been applied in the treatment of this disease [4], and more than 60 protocols have been described. However, when the three most efficacious treatments – corticosteroids, vasodilators and hyperbaric oxygen therapy (HBO_2) – were revised from the Cochrane Collaboration, only the use of HBO_2 received multiple, positive, objective and critical reviews [8].

KEYWORDS:sudden sensorineural hearing loss; hyperbaric oxygen therapy; pressure; audiometry; average hearing threshold

HBO_2 has been used successfully in the management of SSNHL based on the concept that HBO_2 increases the partial pressure of oxygen (pO_2) in the inner ear; improves hemorheology and contributes to improved microcirculation; lowers the hematocrit and entire blood viscosity; and improves erythrocyte elasticity [4, 9]. In addition, research has shown a potential advantage of HBO_2 performed for ISSNHL to increase pO_2 in the blood. By means of diffusion, pO_2 rises in the inner ear fluids which supply the sensory and neural elements in the cochlea. HBO_2 induces cell metabolism in the inner ear, even if the blood supply is insufficient [2, 10, 11].

However, a specific treatment for SSNHL is still missing, and the technical conditions for the use of this method are still unclear. According to the recommendations of the European Consensus Conference on Hyperbaric Medicine 2016 this therapy is recommended within the time of exposure of 90 to 120 minutes at pressures between 2.0 and 2.5 ATA once a day, up to 20 exposures. Reassessment of the patient's condition is recommended after 10 exposures, and pure-tone threshold audiometry results help determine whether the treatment should be discharged or continued for a further 10 exposures. An average hearing gain of more than 10 dB can be used as a selection criterion [12]. The recommended treatment profile by the Undersea and Hyperbaric Medical Society consists of daily sessions breathing 100% O_2 for 90 minutes at 2.0 to 2.5 ATA for 10 to 20 treatments. The 2.4-ATA treatment pressure is probably most practical, especially for facilities with multiplace chamber operations [13].

Most authors who publish in this area manage HBO_2 by a 60- or 90-minute continuous treatment of breathing 100% oxygen once a day for 10 to 20 days – mainly at a pressure of 2.5 ATA (Table 1) [7, 14-29]. In contrast, in our previous study [30] patients underwent a 90-minute HBO_2 treatment once a day for 10 days pressured only at 2.0 ATA. Based on review of the patient's health status after 10 exposures, our experience showed that a 10-exposure treatment was sufficient. The efficiency of both treatment protocols used (control group received steroids supported with hemorheological therapy; the HBO_2 group was treated with additional application of HBO_2) was statistically significant ($p < 0.001$) in both groups of patients, but the supplementation of the therapy with HBO_2 statistically significantly increased the effect of pharmacotherapy ($p < 0.001$) by 11.5 dB up to the final hearing gain of 20 dB.

As we noted, the main purpose of our present study was to compare the efficacy of HBO_2 used in the treatment of SSNHL as a supplementary therapy to the first-line medical treatment according to the different applied pressures used in HBO_2 therapy while maintaining the same number of sessions, periodicity and exposure times.

MATERIALS AND METHODS

In our prospective study we have evaluated the data of 115 patients (59 males, 56 females; mean age of the group 47 ± 15 years). They suffered from SSNHL (IDC-10-CM code H91.2 – Sudden idiopathic hearing loss) within seven days of hearing loss and were admitted to the Department of Otolaryngology, Faculty Hospital Trenčín, Slovakia, between July 2015 and June 2018. The study was approved by the Ethics Committee of the institution under code n. 26210120019. Oral and written information about the study was provided, and informed consent from all patients was obtained before participation.

The patients were grouped according to therapy as those with pharmacotherapy (control group) and those with additional application of HBO_2 (groups H2.0 and H2.5). Not included in the study were: pediatric patients; patients with pre-existing Menière's disease, tumors, barotrauma, acoustic trauma, retrocochlear disease, bilateral hearing loss; patients with a history of chronic otitis in the same ear; and patients with a history of surgery of the same ear. Another inclusion criterion was unilateral sensorineural hearing loss. All patients were hospitalized within seven days of hearing loss and received standard treatment protocol of our department.

Pharmacotherapy consisted of the systematic administration of steroids, supported with hemorheological therapy. For the first five days of hospitalization patients received intravenous application of solumedrol as follows:

- first and second days – 250 mg;
- third and fourth days – 125 mg;
- fifth day – 80 mg ;

Then for the next 10 days the patients received prednisone per oral application:

- sixth to 10th days – 40 mg; and
- 11th to 15th days – 20 mg.

Other medications were: agapurin 2 **x** 100 mg; and betahistine 3 x 16 mg. H2.0 and H2.5 groups underwent a 90-minute continuous treatment of breathing 100% oxygen once a day for 10 days in a multiplace hyperbaric chamber (HAUX-Starmed 2200/2.2S) pressured to 2.0 ATA (H2.0 group) or 2.5 ATA (H2.5 group). Our study was carried out in accordance with the recommendations of the European Consensus Conference on Hyperbaric Medicine 2016:

Table 1 Overview of the variability in the use of HBO_2 treatment protocols for SSNHL

year of the publication	name of the first author	pressure	time of exposure	periodicity	number of sessions	list of references
2018	Toroslu T.	2.0-3.0 ATA	120 min.	once a day	20	[14]
2018	Khater A.	2.0 ATA	60 min.	once a day	20	[15]
2018	Sun H.	2.0 ATA	90 min.	once a day	15	[16]
2018	Xie S.	2.5 ATA	60 min.	twice a day	4-34	[20]
2018	Gülüstan F.	2.5 ATA	120 min.	once a day	21	[21]
2018	Hosokawa S.	2.0 ATA	60 min.	once a day	10	[22]
2017	Ricciardiello F.	2.5 ATA	90 min.	once a day	15-21	[27]
2017	Olex-Zarychta D.	2.5 ATA	60 min.	once a day	15	[17]
2017	Ajduk J.	2.5 ATA	60 min.	once a day	20	[18]
2017	Ergun Taşdöven G.	2.5 ATA	90 min.	once a day	10	[19]
2016	Sevil E.	2.4 ATA	75 min.	once a day	20	[25]
2016	Sherlock S.	2.4 ATA	90 min.	once a day	10	[26]
2016	Lamm H.	2.5 ATA	2x30 min.	once a day	10-33	[23]
2015	Attanasio G.	2.4 ATA	90 min.	twice a day	10	[24]
2015	Psillas G.	2.2 ATA	80 min.	once a day	15	[28]

HBO_2 therapy for SSNHL is recommended for 90 to 120 minutes at pressures between 2.0 and 2.5 ATA once a day, up to 20 exposures with the reassessment of the patient's condition after 10 exposures.

The patients were evaluated by certified audiologists by the standardized methods for pure-tone threshold audiometry (PTA) before and after the treatment. PTA was calculated as an average threshold measured at 250, 500, 1,000, 2,000, 4,000, 6,000, and 8,000 hertz (Hz). Further, the audiological results were defined in terms of three ranges of frequencies: (1) low frequencies (250 – 500 Hz), (2) medium (spoken speech) frequencies (1000 – 2000 Hz) and (3) high frequencies (4000 – 8000 Hz). The treatment responses were divided into two groups: (1) hearing gain (change in PTA) of 10 dB and over (improvement) and (2) hearing gain less than 10 dB (no improvement).

Statistical analysis was performed with the program InStat 3.1 (GraphPad Software, Inc., U.S.). Basic statistical characteristics of the both groups are given by sample size, median, minimum and maximum values. Minimal values can also comprise negative numerical data because they represent therapeutic benefit – i.e. the difference in hearing status before and after therapy. To compare the numerical variables of the three groups of individuals, Kruskal-Wallis non-parametrical test was used with the Dunn's post-test of the partial pairs of groups. Nominal data were processed with the aid of contingency tables based on the chi-square test. In each category, we also calculated the expected numbers of individuals and compared them to the observed numbers. A p-value less than 0.05 was considered to be statistically significant.

As part of the pre-analytical verification of data parameters we tested the rate of benefit of HBO_2 in individuals with hearing impairments of different severity, and we found that the outcome of therapy was not limited within a fixed range.

RESULTS

We evaluated the data for 115 patients with ISSNHL, including 59 men (51.30%) and 56 women (48.70%), with an average age of 49 years (range 20 - 87). The patients were divided into three groups:

- Control group consisted of 35 individuals treated with standard pharmacotherapy;
- H2.0 (49 individuals); and
- H2.5 (31 patients) groups were treated with the same pharmacotherapy and additional HBO_2.

The data presented in Table 2 shows that there was indeed a significant difference in the efficacy of therapeutic methods in terms of overall classification by three

Table 2 Differences in the extent of hearing gain between individuals with H2.0, H2.5 and control groups

frequency (Hz)	*group*	*n*	$\bar{x}$	*sd*	x_m	*min.*	*max.*	*p*	P_D
250-500	H2.0	49	21.9	21.1	18.0	-8	68	0.008	■/-/e*
	H2.5	31	21.1	20.0	18.0	-15	63		-/■/e*
	control	35	8.4	20.1	5.0	-33	65		l*/l*/■
1000-2000	H2.0	49	20.1	18.7	13.0	-10	66	0.03	■/-/e*
	H2.5	31	14.5	20.4	10.0	-20	65		-/■/-
	control	35	9.2	17.6	5.0	-33	53		l*/-/■
4000-8000	H2.0	49	12.5	14.2	13.0	-15	48	0.05	■/-/-
	H2.5	31	13.8	18.7	7.0	-20	53		-/■/-
	control	35	5.8	13.3	3.0	-18	65		-/-/■

n: number of patients $\bar{x}$: arithmetical mean *sd*: standard deviation x_m: median *min.*: minimal value *max.*: maximal value; *p*: probability value of the Kruskal-Wallis test P_D: Dunn´s post-test of the individual pairs of groups: * $P_D < 0.05$; l - statistically significant decreasing; e - statistically significant elevating; - dashes indicate statistical insignificance; ■ - no comparison of the particular group with itself

frequency ranges. The highest arithmetic means and medians can be observed in the H2.0 group, and the lowest means were observed in the control group. The most significant differences can be seen in the 250 to 500 Hz frequency range, where both H2.0 and H2.5 groups were dominant. In the 1000 – 2000 Hz frequency range (spoken speech), only the H2.0 group had statistically significant results, while the H2.5 group compared to the control group was not statistically significant. In the high frequencies of 4,000 – 8,000 Hz, the differences are at the borderline of statistical significance, while the therapeutic benefits were the lowest.

Consequently, we focused on comparing the degree of benefit of treatment among the studied groups. Treatment responses were divided into two groups, the first one with individuals who did not benefit from the therapy: The improvement did not reach a 10 dB difference within this group. The second group consisted of individuals who showed an improvement of 10 dB and over. Subsequently we compared three ranges of analyzed frequencies. The results are shown in the contingency Tables 3–5 that contain two parts. The upper part is computational. In this section, the observed numbers are marked in bold. In brackets, there are expected numbers, which we would expect in the case of absence of differences in the effectiveness of the three therapeutic procedures. The lower part of the tables shows the percentage deviations of the observed abundance from the mathematically expected ones. To sum it up, the greater the absolute value of these numbers (regardless of the sign), the larger the difference between the observed and expected number. The sign indicates the direction, i.e. whether the number of observed individuals is larger (+) or smaller (-) than the expected number counted mathematically.

The data presented in Table 3 shows the comparison of therapeutic response in the 250 – 500 Hz frequency range. The H2.5 group clearly dominated, with improved hearing gain in +27.3% patients based on the assumption, that all therapeutic approaches have the same effectiveness. The second best treatment response was observed in the H2.0 group. In contrast, pharmacotherapy without HBO_2 exposures (control group) had impact on -26.2% of patients.

Table 4 contains statistical evaluation of the efficacy of therapeutic modalities on the 1,000 – 2,000 Hz frequency range (spoken speech) with the null hypothesis of the statistical test was again based on the presumption of the quantitatively identical effect of the three therapeutic approaches. Even in this case, our assumption has not been confirmed. The H2.0 group was evaluated as the most effective therapeutic intervention (+20.9%). Interestingly, in the H2.5 group balanced results were observed, slightly disposed toward the detriment of its effectiveness.

In the high-frequency range of 4,000 – 8,000 Hz the H2.0 group clearly dominated by its success rate (+33.7% in addition to the expected counts of individuals with therapeutic benefit), followed by the H2.5 group. The pharmacotherapy without HBO_2 (control group) has traditionally been shown to be the least effective, with only -64.3% observed counts compared to theoretically expected numbers (Table 5).

Table 3: Therapeutic gain in frequency range 250 – 500 Hz

Range of frequencies 250-500 Hz	No improvement	Improvement	Total
H2.0	**18** (20.45)	**31** (28.55)	49
H2.5	**8** (12.94)	**23** (18.06)	31
Control	**22** (14.61)	**13** (20.39)	35
Total	48	67	115

χ^2=10.16, *d.f.*=2; p=0.006. Expected numbers are shown in brackets. Observed frequencies are in **bold**.

Range of frequencies 250-500 Hz	No improvement	Improvement	
H2.0	-12%	+8.6%	Percentage deviations in individual cells: % = (observed - expected) / expected x 100
H2.5	-38.2%	+27.3%	
Control	+50.6%	-36.2%	

Table 4. Therapeutic gain in frequency range 1,000 – 2,000 Hz

Range of frequencies 1,000-2,000 Hz	No improvement	Improvement	Total
H2.0	15 (20.88)	34 (28.12)	49
H2.5	14 (13.21)	17 (17.79)	31
Control	20 (14.91)	15 (20.09)	35
Total	49	66	115

χ^2=5.99, *d.f.*=2; p=0.05. Expected numbers are shown in brackets. Observed frequencies are in **bold**.

Range of frequencies 1,000-2,000 Hz	No improvement	Improvement	
H2.0	-28.2%	+20.9%	Percentage deviations in individual cells: % = (observed - expected) / expected x 100
H2.5	+6.0%	-4.4%	
Control	+34.1%	-25.3%	

Table 5. Therapeutic gain in frequency range 4,000 – 8,000 Hz

Range of frequencies 4,000-8,000 Hz	No improvement	Improvement	Total
H2.0	22 (28.80)	27 (20.20)	49
H2.5	16 (18.22)	15 (12.78)	31
Control	29 (19.98)	5 (14.02)	34
Total	67	47	114

χ^2=14.42, *d.f.*=2; p=0.001. Expected numbers are shown in brackets. Observed frequencies are in **bold**.

Range of frequencies 4,000-8,000 Hz	No improvement	Improvement	
H2.0	-23.6%	+33.7%	Percentage deviations in individual cells: % = (observed - expected) / expected x 100
H2.5	-12.2%	+17.4%	
Control	+45.1%	-64.3%	

DISCUSSION

Existing literature on HBO_2 for SSNHL includes studies that utilized various different treatment pressures ranging from 1.5 ATA to 3.0 ATA [7,14-29]. In their study Uzun, et al. [29] discovered practice differences in the treatment of SSNHL with HBO_2 among European hyperbaric centers through a nine-question survey completed by the medical directors of HBO_2 centers. Altogether 192 centers were invited to take part in the study: 80 (41.6%) centers from 25 countries responded. A total of 70 centers of 80 were using HBO_2 for SSNHL: 43 of 56 used one session a day, while 13 centers reported that they used sessions twice a day for at least part of the HBO_2 course. Of these, 10 were using HBO_2 twice a day exclusively in the first three to five days, and afterward they shifted to once-daily exposures. Total number of HBO_2 sessions delivered per patient ranged from five to 40. Treatment duration varied between 60 and 140 minutes, and treatment pressure between 1.5 and 2.5 ATA, respectively. The majority of centers (48/56) were using a treatment pressure of 2.4/2.5 ATA, four were using 2.0 ATA, two 1.8 ATA and two others 1.5 ATA. Twenty-nine of 56 centers reported using between 90 and 105 minutes of HBO_2, 20 between 120 and 140 minutes, and seven 60 to 75 minutes of HBO_2. The most frequently used treatment protocol was 90 minutes at 2.4/2.5 ATA by 19 of 56 centers. Furthermore, 44 of 55 centers expressed their interest in participating in studies that would compare the effectiveness of different HBO_2 protocols in treating SSNHL.

There were published papers in which HBO_2 had an important function in the group of patients with SSNHL in whom primary treatment with corticosteroids did not reach overall improvement of hearing. In these cases HBO_2 was administered as a "rescue therapy"

within three months of the onset of hearing impairment. Czech authors treated a small group of patients using rescue HBO_2 therapy (3 ATA / 90 minutes / 10 sessions / once a day) initiated 30 to 60 days (average 44 days) from onset of ISSNHL. Patients had previous ineffective vasodilating infusion and corticosteroid therapy. Within this set of HBO_2-treated patients, significant improvement at frequencies of 1,000 Hz and 2,000 Hz was apparent [31].

To our best knowledge, there has been only one study that compared the effectiveness of HBO_2 at different treatment pressures [32]. In this retrospective study, mean hearing gain levels in patients who received no HBO_2 or HBO_2 at 1.5 ATA were similar (2.6 ± 15 dB and 3.1 ± 9 dB respectively), but was significantly better with HBO_2 at 2.5 ATA (19.7 ± 23 dB). Because the baseline peripheral arterial tonometry levels (no HBO_2 32.5 ± 26.3 dB; HBO_2 at 1.5 ATA 32.3 ± 27.8 dB; HBO_2 at 2.5 ATA 76 ± 27.5 dB) differed significantly between the groups, a firm conclusion could not be deduced from this study. In this study we would like to draw attention to the fact that this study was carried out as a salvage therapy for SSNHL, while the aim of our study was the first-line medical treatment (within seven days of hearing loss). Authors concluded that HBO_2 at 2.5 ATA in patients with SSNHL after unsuccessful conventional treatment yields significant improvement of hearing, but the mean hearing gain is higher when time delay before HBO_2 is shorter.

Regarding possible mechanisms for the positive results achieved, some aspects are discussed. Corticosteroids are still the mainstay of treatment for SSNHL, with statistically provable effects especially on medium frequencies (spoken speech). Their effect is important to improve microvascular circulation, decrease inflammation processes in the inner ear, and to suppress the immune response [30]. Randomized controlled trials concerning the benefit of anti-inflammatory treatment with corticosteroids in patients with SSHNL are contradictory in outcome. A meta-analysis published and recently updated in the Cochrane library concludes that the value of steroids in the treatment of ISSNHL remains unclear [33]. The predicted mechanism of HBO_2 action is to increase the partial pressure of oxygen in the blood, which in turn increases the partial pressure of oxygen through diffusion in the inner ear fluids [30]. A synergistic effect of steroids and HBO_2 has been proposed in order to explain the gain of threshold. On one side, steroids reduce inflammation in the inner ear that may be contributing to hearing loss, while on the other, HBO_2 increases intracochlear aid in the recovery of hearing. Furthermore the synergistic effect of steroids and HBO_2 is the reduction of edema in the inner ear. Lamm, et al. [33] assume that HBO_2 changes the permeability of the round window membrane that allows the increase influx of steroids by intratympanic steroid application into the perilymph, especially into the basal turn of the cochlea. This may explain the recovery of hearing not only in the low frequencies but also in the high frequencies that are more refractory to recovery treatment. Furthermore, the partial pressure of oxygen in the scala tympani achieved by HBO_2 in an experimental setting increased the protection of neurosensory cells and restoration of the oxidative metabolism in the vascular strip. In addition, HBO_2 improves rheology and microcirculation by lowering the blood viscosity and improving erythrocyte elasticity.

Our results suggest significant favorable impact of HBO_2 on the overall healing process at all the tested frequencies. If we evaluate the profit of the therapy, in the case of a quantitative comparison of the average therapeutic gains on tested frequency ranges, we find statistically significant differences in both HBO_2 groups compared to the control group. In terms of median sizes (non-parametric tests were used) in the medium- and high-frequency ranges (1,000 – 2,000 Hz and 4,000 – 8,000 Hz), the hearing gains of the H2.0 group show the dominance in the form of maximal remedial benefit. On the other hand, in the low-frequency range of 250 – 500 Hz, the results of both HBO_2 groups that used the pressures of 2.0 ATA and 2.5 ATA, respectively, were very similar statistically.

If we consider results from the perspective of categories we obtain interesting results. We divided obtained data in all tested groups into two categories. The applied therapeutic approach:

- "did not help" (i.e., hearing gain less than 10 dB; no improvement); or
- "helped" (i.e., change in PTA of 10 dB and over; improvement).

Again, we find statistically significant differences of both HBO_2 groups compared to the control group in all the tested frequency ranges. In the 250 – 500 Hz range the best hearing gains were obtained in the H2.5 group, but in two higher frequency ranges (1,000 – 2,000 Hz and 4,000 – 8,000 Hz, respectively) the best therapeutic response was observed in the H2.0 group.

The above results represent the key period necessary to optimize the conditions of application of supplementary HBO_2 therapy in treatment of SSNHL. To summarize, patients in the H2.5 group were exposed to a 90-minute

HBO_2 treatment once a day for 10 days at 2.5 ATA, while patients in the H2.0 group were treated using the same protocol but at 2.0 ATA. The effectiveness of HBO_2 in the treatment of SSNHL at different treatment pressures was different between these two groups. At low frequencies (250 – 500 Hz), the use of 2.5 ATA pressure was more efficient than 2.0 ATA. However, in the higher frequency ranges (1,000 – 2,000 Hz and 4,000 – 8,000 Hz), the better hearing gains were obtained at 2.0 ATA pressure. The obtained 2.0 ATA positive results may be in accordance with the results of several experimental works on the effect of HBO_2 on central nervous system damage. According to these works glucose metabolism is optimal at 1.5 – 2.0 ATA, with concurrent cerebral blood flow and intracranial pressure decrease at 2.0 ATA. Also observed was the balance between the production of O_2 radicals and antioxidant capacity as well as the optimal balance between benefit and risk of hyperoxia [34-37].

Our results support the possibility to optimize the use of HBO_2 in SSNHL treatment to individually meet each person´s needs. The applied technical conditions (pressure, number of sessions, periodicity and exposure times) should depend on the type and frequency range of hearing impairment (shape of the audiogram) in favor of using 2.0 ATA. This is very important in terms of taking an individual approach to each patient while noting the degree of his or her illness. It also helps to minimize the burden of a patient in order to obtain the maximum beneficial effect of the therapy.

However, our findings open other key questions for the future: *What should be the optimal concentration of the steroids used? What are the key factors in the pre-treatment process of patients that can positively or negatively influence the resulting therapeutic effect?* Further investigations are warranted to explore the mechanisms of action in the treatment of SSNHL.

CONCLUSIONS

In the view of the quantitative assessment of efficacy of HBO_2 based on the results of our study we can conclude the following: There is a notable difference in the therapeutic effect of HBO_2 according to different applied pressures while maintaining the same number of sessions, periodicity and exposure times. Further comprehensive clinical trials are needed in the development of standardized therapeutic procedures with defined sequences of treatment interventions and estimated range of laboratory-determined parameters. The task for our project is to add the missing data to this area of knowledge with emphasis on the needs of the local population.

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FROM THE HBO_2 INDICATIONS MANUAL14TH EDITION:
CHAPTER 1

Hyperbaric treatment of air or gas embolism: current recommendations

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ABSTRACT

Gas can enter arteries (arterial gas embolism, AGE) due to alveolar-capillary disruption (caused by pulmonary over-pressurization, e.g. breath-hold ascent by divers) or veins (venous gas embolism, VGE) as a result of tissue bubble formation due to decompression (diving, altitude exposure) or during certain surgical procedures where capillary hydrostatic pressure at the incision site is subatmospheric. Both AGE and VGE can be caused by iatrogenic gas injection. AGE usually produces stroke-like manifestations, such as impaired consciousness, confusion, seizures and focal neurological deficits. Small amounts of VGE are often tolerated due to filtration by pulmonary capillaries; however VGE can cause pulmonary edema, cardiac "vapor lock" and AGE due to transpulmonary passage or right-to-left shunt through a patient foramen ovale. Intravascular gas can cause arterial obstruction or endothelial damage and secondary vasospasm and capillary leak. Vascular gas is frequently not visible with radiographic imaging, which should not be used to exclude the diagnosis of AGE. Isolated VGE usually requires no treatment; AGE treatment is similar to decompression sickness (DCS), with first aid oxygen then hyperbaric oxygen. Although cerebral AGE (CAGE) often causes intracranial hypertension, animal studies have failed to demonstrate a benefit of induced hypocapnia. An evidence based review of adjunctive therapies is presented.

Air or gas embolism mechanisms

Gas embolism occurs when gas bubbles enter arteries or veins. AGE was classically described during submarine escape training, in which pulmonary barotrauma occurred during free ascent after breathing compressed gas at depth. Pulmonary barotrauma and gas embolism due to breath holding can occur after an ascent of as little as 1 meter [1]. AGE has been attributed to normal ascent in divers with lung pathology such as bullous disease and asthma [2-3]. Pulmonary barotrauma can also occur as a result of blast injury in or out of water [4-6].

Iatrogenic AGE is due to accidental direct intra-arterial injection of gas. Venous injection of small amounts of gas is not usually problematic because small volumes of VGE bubbles are normally filtered by the pulmonary capillaries and do not cause clinical symptoms. However, in large volumes VGE can cause endothelial injury in pulmonary capillaries and cough, dyspnea and pulmonary edema [7-8]. The capacity of the pulmonary capillary network can also be overwhelmed by large volumes of venous gas, allowing bubbles to enter the arterial circulation [9-10]. VGE can also enter the left heart directly via an atrial septal defect or patent foramen ovale [11-14].

Asymptomatic venous gas embolism (VGE) commonly occurs after compressed gas diving15-16 and after rapid exposure to altitude [17], such as during flight in a military jet, in a hypobaric chamber, or with accidental loss of pressure during flight in commercial aircraft. VGE can occur due to passive entry of air into surgical wounds that are elevated above the level of the heart (such that the pressure in adjacent veins is subatmospheric) [18].

Clinical deficits can occur after intra-arterial injection of only small volumes of air, while intravenous air injection is often asymptomatic. Injection of up to 0.5-1 mL/kg has been tolerated in experimental animals [19]. In humans, continuous IV infusion of oxygen at 10 mL/minute has been reported as well tolerated, while 20 mL/minute has been reported to cause symptoms [20]. Compared with constant infusions, bolus injections are more likely to cause clinical abnormalities [21].

There are several possible mechanisms of injury,

KEYWORDS: arterial gas embolism; air embolism; hyperbaric oxygen

including intracardiac "vapor lock," with resulting hypotension or acute circulatory arrest, and direct arterial occlusion. Animal studies using a cranial window have demonstrated that bubbles can cause a progressive decline in cerebral blood flow [22-23] even without vessel occlusion, an effect that requires neutrophils [24] and can be initiated by bubble-induced stripping of the endothelium from the underlying basement membrane [25-27]. Even without direct mechanical damage, bubble contact with endothelial cells can initiate opening of transient receptor potential vanilloid (TRPV) ion channels, calcium entry, mitochondrial dysfunction and cell death [28-30]. In some cases of cerebral AGE there is clinical improvement followed by delayed deterioration a few hours later [31]. Proposed mechanisms for this include edema, bubble regrowth and secondary thrombotic occlusion.

Manifestations

Manifestations of arterial gas embolism include loss of consciousness, confusion, focal neurological deficits, cardiac arrhythmias or ischemia, while venous gas embolism may include hypotension, tachypnea, hypocapnia, pulmonary edema or cardiac arrest [32-37]. AGE in divers usually presents within a few minutes of surfacing, with cerebral manifestations such as hemiparesis, confusion or loss of consciousness. When the diver has been underwater for a time sufficient to incur a significant inert gas load, gas embolism can precipitate neurological manifestations that are more commonly seen with DCS, such as paraplegia, due to spinal cord damage [38].

Features that support the diagnosis of AGE include rapid or breath-hold ascent or evidence of pulmonary barotrauma (in a diver), evidence of intravascular gas using ultrasound, direct observation (e.g., aspiration of gas from a central venous line) or circumstances consistent with gas embolism occurrence. While imaging studies sometimes reveal intravascular air, brain imaging is often normal even in the presence of severe neurological abnormalities [39-43].

Clinical management and rationale for hyperbaric treatment

Recognition. The presumptive diagnosis of AGE is made on the basis of clinical criteria. Diagnostic imaging is unnecessary, has low diagnostic sensitivity [4]3 and does not affect management. Absence of intravascular gas should not prevent treatment. Neither CT nor MRI are therefore recommended to attempt to confirm a diagnosis. Performing brain imaging when there is a high degree of suspicion of AGE usually delays the initiation of appropriate HBO_2 treatment and only serves a useful clinical purpose if other pathology is detected that requires different treatment. The only rational reason to perform diagnostic imaging is to exclude other pathology that might have similar manifestations as AGE but require different management (e.g., intracranial hemorrhage).

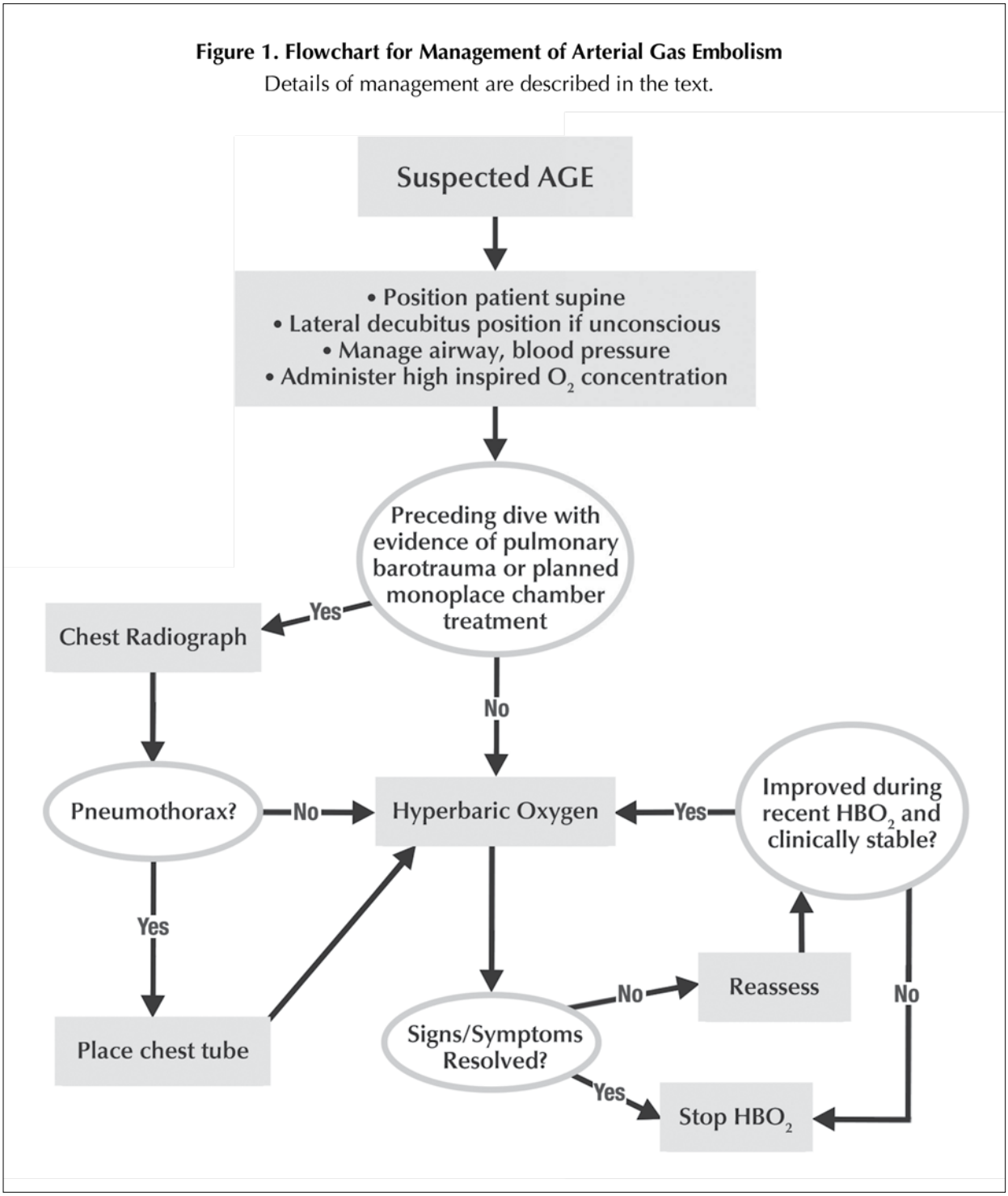
First Aid. Immediate treatment of gas embolism should consist of airway management, maintenance of blood pressure and administration of as high an oxygen concentration as is feasible. Hypotension can augment the injury and should be actively treated [44]. Supplemental oxygen is recommended not only to maintain arterial oxygenation, but also to facilitate bubble resorption. Nitrous oxide (N_2O) administration causes bubbles to grow, and if gas embolism is suspected in an anesthetized patient N_2O should be discontinued in favor of 100% oxygen.

Head-down position was formerly recommended for the initial treatment of patients with AGE, in order to minimize the risk of additional cerebral embolization because of buoyancy, and shrinkage of bubbles due to increased hydrostatic pressure, and some anecdotal cases support its use [45]. Lateral decubitus position has been recommended in the past for first aid treatment of VGE; however, buoyancy has little if any effect upon arterial [46] or venous [47] distribution of intravascular air. Furthermore, the head-down position can worsen cerebral edema [48]. Head-down position is no longer recommended [49-50]. Recommended first aid for AGE includes placing the patient in the supine position. Unconscious patients should ideally be positioned to maximize airway protection and management: the recovery (lateral decubitus) position [49-50].

Hyperbaric oxygen. HBO_2 to treat gas embolism remains the definitive treatment for arterial gas embolism [51-52] due to the effect of higher ambient pressure to reduce bubble volume, an increase in tissue oxygenation induced by HBO_2 and pharmacological effects of hyperbaric hyperoxia that include inhibition of leukocyte adhesion to damaged endothelium [53-54]. Reviews of published cases of arterial gas embolism reveal superior outcomes with the use of HBO_2 compared to non-recom-pression treatment [32, 36, 55-65]. A short interval between embolism and recompression treatment is associated with a higher probability of good outcome. However, a response to treatment has been observed after 24 or more hours [66]. HBO_2 treatment is not required for asymptomatic VGE; however it has produced clinical improvement in patients with the sole manifestation of secondary pulmonary edema [67].

Figure 1. Flowchart for Management of Arterial Gas Embolism

Details of management are described in the text.



Because of the tendency for patients with AGE to deteriorate after apparent recovery [31], early HBO_2 is recommended even for patients who appear to have spontaneously recovered. One author has suggested that the presence or absence of air detectable by brain computed tomography should be used as a criterion for HBO_2 therapy [68]. However, timely administration of HBO_2 usually causes clinical improvement even in the absence of demonstrable air, possibly due to the effect of HBO_2 to attenuate leukocyte adherence to damaged endothelium [54] and secondary inflammation, and thus facilitate return of blood flow.

In patients with AGE caused by pulmonary barotrauma there may be a coexisting pneumothorax, which could develop into tension pneumothorax during chamber decompression. Therefore, placement of a chest tube in patients with pneumothorax prior to HBO_2 should be considered and is recommended for patients treated in a monoplace chamber. For multiplace chamber treatment, careful monitoring is a feasible option. Coexisting pneumomediastinum does not generally require any specific therapy and will usually resolve during HBO_2.

Immediate recompression to 6 atmospheres absolute (ATA) was recommended in the past. However, there is no conclusive evidence that pressures higher than 2.82 ATA (18 msw, 60 fsw) offer any advantage. If possible, an initial compression to 2.82 ATA (60 fsw or 18 msw equivalent depth) breathing 100% oxygen is recommended, using USN Treatment Table 6 or equivalent. The standards against which other treatment schedules ("tables") should be compared are those of the U.S. Navy (USN Diving Manual [69], available at *http://www.supsalv.org/*) and similar procedures used by other navies and commercial diving operations [70-71]. Shorter tables designed for use in monoplace chambers have been used with success [72]. Significant modification of established HBO_2 treatment regimens have been used in facilities and personnel with the necessary expertise and hardware [70], such that if the clinical response to treatment is judged to be suboptimal, options including deeper recompression or extension of the treatment table can be instituted according to the expertise and resources available.

Administration of repetitive treatments is recommended until there is no further stepwise improvement, typically after no more than one to two hyperbaric treatments, but occasionally up to five to 10 [70-71,73].

More detailed reviews of adjunctive therapies are available in other publications [71,74-76], and a summary can be obtained on the Undersea and Hyperbaric Society website (*www.uhms.org/images/Publications/ ADJUNCTIVE_THERAPY_FOR_DCI.pdf*). Specific adjunctive therapies and their recommendations are listed below.

Adjunctive therapy

Adjunctive therapies for isolated AGE include the following:

- oxygen administered as a first aid measure (class I, level C)
- lidocaine (class IIa, level B)
- aspirin, NSAIDs (class IIb, level C)
- anticoagulants (class IIb, level C)
- corticosteroids (class III, level C)
- intravenous fluids (D5W class III, level C; isotonic crystalloid, colloid class IIb, level C)

Hyperglycemia should be treated, as it worsens acute CNS injury. Although isolated AGE does not require specific fluid therapy, patients with accompanying decompression sickness may have significant hemoconcentration, and require aggressive fluid resuscitation (see Chapter 7: Decompression Sickness in the 14th edition of the HBO_2 indications book). For patients who are immobilized for 24 hours or longer due to neurological injury, low molecular weight heparin is recommended for prophylaxis against venous thromboembolism (class I, level A). In addition, since hyperthermia can adversely affect neurological outcome, aggressive treatment of fever is recommended. There is a plausible rationale for induced hypothermia, which is not yet standard of care but has been reported for AGE due to lung biopsy [77] and in conjunction with HBO_2 for AGE after scuba diving [78]. For critically ill patients with AGE, no systematic human studies are available. In combination with HBO_2, large-animal studies support the use of normotension and isocapnia [44,79-80].

Outcome

While there are no published controlled studies of HBO_2 for AGE, in a retrospective review of 656 published AGE cases, Dutka reported full recovery in 78% of 515 individuals who received HBO_2 vs. 56% of 141 who did not [64]. In the same series the mortality rates were, respectively, 5% and 42%. Of 19 patients reported by Benson with iatrogenic AGE referred for hyperbaric therapy, after the first treatment five patients (26%) resolved all signs and symptoms, 11 (58%) exhibited improvement, one (5%) had no change and two (11%) were not assessable secondary to medically induced paralysis [43]. Within two months post-HBO_2 three additional patients had resolved completely, and six showed further improvement. Eight patients (42%) had complete recovery, six (32%) had partial recovery, and five patients (26%) died of complications of AGE.

In a series of 45 patients treated with HBO_2 for AGE within a single institution reported by Beevor, good neurological outcome (extended Glasgow outcome scale 7 or 8) was achieved in 27 (60%) [81]. The only statistically significant factor predictive of good outcome was time to HBO_2 treatment (good outcome mean 8.8 hours vs.16.5 hours). However, gas bubbles have been known to persist for several days, and there are many reports noting success when HBO_2 treatments were begun after delays of hours to days [61,65,82-83]. In the series reported by Benson, one patient had eventual complete recovery despite a 28-hour time from incident to HBO_2 [43]. In a case

TABLE 1. CAUSES OF ARTERIAL GAS EMBOLISM

DIRECT ARTERIAL AIR ENTRY
Pulmonary barotrauma during ascent from a dive [85]
Mechanical ventilation [86]
Penetrating chest trauma [87]
Chest tube placement [88, 89]
Needle biopsy of the lung [90, 91]
Bronchoscopy [92]
Cardiopulmonary bypass accident [93-95]
Pulmonary bulla rupture during altitude exposure [96-98]
Accidental air injection into a radial artery catheter [99-102]
Vascular air entry due to necrotizing pneumonia [103]
Pulmonary barotrauma from blast injury [157]
Pulmonary overinflation from inhalation of gas under high pressure [158]

VENOUS GAS EMBOLISM WITH SECONDARY ARTERIAL ENTRY VIA PULMONARY CIRCULATION OR INTRACARDIAC RIGHT-TO-LEFT SHUNT
Compressed gas diving [7-10, 15-16]
Rapid exposure to altitude [17]
Accidental intravenous air injection [104-105]
Hemodialysis catheter accident [106]
Central venous catheter placement or disconnection [107-108]
Gastrointestinal endoscopy [109-110]
Esophageal ballooning and endoscopic retrograde cholangiopancreatography [111]
Hydrogen peroxide irrigation [89, 112-118]
Arthroscopy [119-120]
Cardiopulmonary resuscitation [121]
Percutaneous hepatic puncture [122]
Blowing air into the vagina during orogenital sex [61, 123-124]
Sexual intercourse after childbirth [125-126]
Gastric barotrauma following hyperbaric oxygen therapy [127]
Treatment of esophageal cancer128-129]
Atrial-esophageal fistula following ablation for atrial fibrillation [130-133]

PROCEDURES IN WHICH THE SURGICAL SITE IS UNDER PRESSURE
Laparoscopy [134-138]
Transurethral surgery [139-140]
Vitrectomy [141]
Endoscopic vein harvesting [142]
Hysteroscopy [143-144]

PASSIVE ENTRY OF AIR INTO SURGICAL WOUNDS SITUATED ABOVE THE LEVEL OF THE HEART SUCH THAT VENOUS PRESSURE IS SUBATMOSPHERIC [18]
Sitting craniotomy [145]
Cesarean section [146]
Radical perineal prostatectomy [147]
Retropubic prostatectomy [148-149]
Spine surgery [150-151]
Hip replacement [152]
Liver resection [153]
Liver transplantation [154]
Insertion of dental implants [155-156]

report of a 51-year-old diver who lost consciousness within minutes of a 30-meter dive, he remained deeply comatose, intubated and with cardiovascular instability for six days before HBO_2 could be administered. One year after treatment he was leading a functional life [84].

Evidence-based review

The use of HBO_2 for arterial gas embolism and symptomatic venous gas embolism is an AHA class I recommendation (level of evidence C).

Utilization review

Utilization review is recommended after 10 treatments.

Cost impact

The primary treatment of choice for air embolism from any cause is HBO_2 therapy. Decreased high mortality rates and prevention or moderation of permanent neurological damage make this modality cost-effective.

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FROM THE HBO_2 INDICATIONS MANUAL14TH EDITION:
CHAPTER 7

Hyperbaric treatment for decompression sickness: current recommendations

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Rationale

Decompression sickness (DCS, "bends") is caused by formation of bubbles in tissues and/or blood when the sum of dissolved gas pressures exceeds ambient pressure (supersaturation) [1]. This may occur when ambient pressure is reduced during any of the following:

- ascent from a dive;
- depressurization of a hyperbaric chamber;
- rapid ascent to altitude in an unpressurised aircraft or hypobaric chamber;
- loss of cabin pressure in an aircraft [2] and
- during space walks.

In diving, compressed gas breathing is usually necessary, although rarely DCS has occurred after either repetitive or very deep breath-hold dives [3, 4]. Although arterial gas embolism due to pulmonary barotrauma can occur aftera dive as shallow as 1 meter, the threshold depth for DCS in compressed-gas diving is around 20 feet of seawater (fsw) [5]. DCS after a dive can be provoked by mild altitude exposure, such as a commercial aircraft flight [6,7], but without a preceding dive the threshold altitude for DCS occurrence in unpressurized flight is 18,000-20,000 feet [8,9].

Several mechanisms have been hypothesized by which bubbles may exert their deleterious effects. These include:

- direct mechanical disruption of tissue [10];
- occlusion of blood flow, platelet deposition and activation of the coagulation cascade [11];
- endothelial dysfunction [12-13];
- capillary leakage [14-18];
- endothelial cell death, complement activation [19,20];
- inflammation [21]; and
- leukocyte-endothelial interaction [22].

Recent evidence suggests that circulating microparticles may play a pro-inflammatory role in DCS pathophysiology [23,24].

The diagnosis of DCS is made on the basis of careful evaluation of the circumstances of the dive (or altitude exposure), the presence of known risk factors, and the post-dive latency and nature of the manifestations [25-28]. DCS manifestations most commonly include paresthesias, hypesthesia, musculoskeletal pain, skin rash and malaise [25-28]. Less common but more serious signs and symptoms include motor weakness, ataxia, vertigo, hearing loss, dyspnea, pulmonary edema [29], bladder and anal sphincter dysfunction, shock and death [25-28]. Severe DCS may be accompanied by hemoconcentration, hypotension and coagulopathy [17, 30]. Severe symptoms usually occurwithin one to three hours of decompression; the vast majority of all symptoms manifest within 24 hours, unless there is an additional decompression (e.g., altitude exposure) [27]. Altitude DCS has similar manifestations, although cerebral manifestations seem to occur more frequently [27].

Investigations have limited value in diagnosis of DCS. Chest radiography prior to hyperbaric oxygen (HBO_2) treatment in selected cases may be useful to exclude pneumothorax (which may require tube thoracostomy placement before recompression). If the clinical presentation is not typical of DCS or notably inconsistent with the circumstances of the dive, neural imaging is occasionally useful to exclude causes unrelated to diving for which treatment other than HBO_2 would be appropriate (e.g., herniated disc or spinal hemorrhage). However, imaging studies are rarely helpful for the evaluation or management of DCS [31, 32]. Magnetic resonance imaging is not sufficiently sensitive to consistently detect early anatomic correlates of neurological DCI [33, 34]. Bubbles causing limb pain cannot be detected radiographically. Neither imaging nor neurophysiological studies should be relied upon to confirm the diagnosis of DCS or be used in deciding whether a patient with suspected DCS needs HBO_2.

KEYWORDS: decompression sickness; bends; hyperbaric oxygen

Improvement of decompression sickness symptoms as a result of recompression was first noted in the 19th century [35]. Recompression with air was first implemented as a specific treatment for that purpose in 1896 [36]. Oxygen breathing was observed by Bert in 1878 to improve the signs of decompression sickness in animals [37]. The use of oxygen with pressure to accelerate gas diffusion and bubble resolution in humans was first suggested in 1897 [38] and eventually tested in the 1930s for human DCS and recommended for the treatment of divers [39]. The rationale for treatment with HBO_2 includes immediate reduction in bubble volume, increasing the diffusion gradient for inert gas from the bubble into the surrounding tissue, oxygenation of ischemic tissue and reduction of CNS edema. It is also likely that HBO_2 has other beneficial pharmacological effects, such as a reduction in neutrophil adhesion to the capillary endothelium [40,41]. The efficacy of HBO_2 is now widely accepted, and HBO_2 is the mainstay of treatment for this disease [27,42-47].

Patient selection criteria

Treatment is recommended for patients with a history of a decompression and whose manifestations are consistent with DCS. HBO_2 treatment is recommended for all patients with symptoms of DCS whenever feasible, although normobaric oxygen administration may be sufficient for the treatment of altitude DCS when neurological manifestations are absent, and for mild DCS (as defined below) following diving. For definitive treatment of altitude-induced cases that do not respond to ground-level oxygen, and for more serious cases of DCS after diving, HBO_2 remains the standard of care [44,45,48-49].

At a consensus workshop on remote treatment of mild DCS (limb pain, constitutional symptoms, subjective sensorysymptoms or rash, with non-progressive symptoms, clinical stability for 24 hours or more and a normal neurological exam), it was concluded that some patients with mild symptoms and signs after diving can be treated adequately without recompression [50]. Thus, although HBO_2 remains the preferred intervention in all cases of DCS, not least because DCS may recover more slowly without recompression [50] it is acceptable to treat cases fitting the mild classification with first aid measures (see below) alone if access to HBO_2 is logistically difficult or hazardous. Such decisions should be made on a case-by-case basis only and must always involve a diving medicine physician [51].

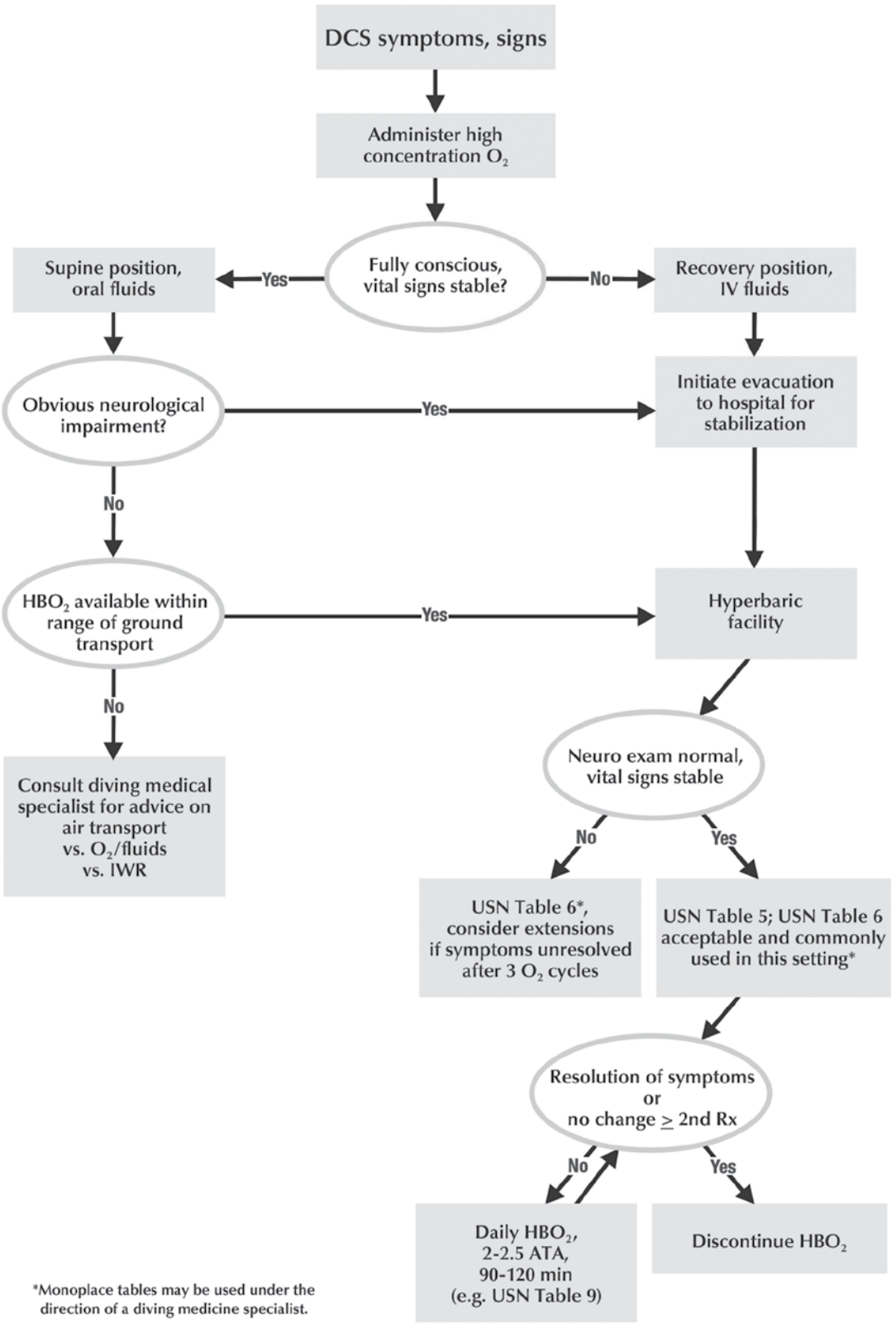
Clinical management

First aid. In addition to general supportive measures, including fluid resuscitation, airway protection and blood pressure maintenance, administration of 100% oxygen at ground level (1 atmosphere absolute [ATA]) is recommended as first aid for all cases of DCS. Normobaric oxygen can be definitive treatment for altitude-induced DCS [51,52].

The following consensus guidelines for pre-hospital care have been developed by a group of international physicians organized by the Divers Alert Network [51].

- Normobaric oxygen (surface oxygen administered as close to 100% as possible) is beneficial in the treatment of DCI. Normobaric oxygen should be administered as soon as possible after onset of symptoms.
- Training of divers in oxygen administration is highly recommended.
- A system capable of administering a high percentage of inspired oxygen (close to 100%) and an oxygen supply sufficient to cover the duration of the most plausible evacuation scenario is highly recommended for all diving activities. In situations where oxygen supplies are limited and where patient oxygenation may be compromised (such as when drowning and DCI coexist), consideration should be given to planning use of available oxygen to ensure that some oxygen supplementation can be maintained until further supplies can be obtained.
- A horizontal position is generally encouraged in early presenting DCI and should be maintained during evacuation if practicable. The recovery position is recommended in unconscious patients. The useful duration of attention to positioning in DCI is unknown. The head-down (Trendelenburg) position is no longer recommended in management of DCI.
- Oral hydration is recommended but should be avoided if the patient is not fully conscious. Fluids should be non-carbonated, non-caffeinated, non-alcoholic and ideally an electrolyte-containing oral resuscitation fluid such as WHO oral rehydration solution or Pedialyte™ (but drinking water is acceptable).
- If suitably qualified and skilled responders are present, particularly in severe cases, intravascular rehydration (intravenous or intraosseous access) with non-glucose containing isotonic crystalloid is preferred. Intravenous glucose-containing solutions should not be given.
- Treatment with a nonsteroidal anti-inflammatory drug (NSAID) is appropriate if there are no contra-indications.

Figure 1. Flowchart for DCS Symptoms
Details of management are described in the text.



- Other agents such as corticosteroids, pentoxifylline, aspirin, lidocaine and nitroglycerine have been utilized by suitably qualified responders in early management of DCI, but there is insufficient evidence to support or refute their application.
- Divers should be kept thermally comfortable (warm but not hyperthermic). Hyperthermia should be avoided especially in cases with severe neurological signs and symptoms. For example, avoid exposure to the sun, unnecessary activity or excess clothing.

Hyperbaric oxygen. Recommended treatment of DCS is administration of oxygen at suitable pressures greater than sea level (hyperbaric oxygen). The choice of treatment table and the number of treatments required will depend upon the following: (a) the clinical severity of the illness; (b) the clinical response to treatment; and (c) residual symptoms after the initial recompression. A wide variety of initial hyperbaric regimens have been described, differing in treatment pressure and time, partial pressure of oxygen and diluent gas. Although there are no humanoutcome data obtained in prospective, randomized studies for the treatment of diving-related decompression sickness, broad principles that are generally agreed upon include the following: (a) complete resolution is more likely to result from early hyperbaric treatment [27,44]; (b) the U.S. Navy (USN) oxygen treatment tables [49] (and the similar RN and Comex tables), with initial recompression to 60 fsw (18 msw, 2.82 ATA) have been the most widely used recompression procedures for DCS treatment beginning at the surface, and have achieved a high degree of success in resolving symptoms [27,43,46,47,52,53], Treatment at shallower depths (e.g., 33 fsw, 10 msw, 2 ATA) can also be effective, although published case series suggest that the success rate may be lower at treatment depths less than 60 fsw [46,54].

Treatment depth exceeding 60 fsw (18 msw). For the vast majority of cases of DCS, superiority of treatments at pressure exceeding 2.82 ATA or using helium as the diluent gas has not been demonstrated [55]. The speculative use of treatment schedules that deviate from the U.S. Navy oxygen treatment tables or published monoplace tables are best reserved for facilities and personnel with the experience, expertise and hardware necessary to deal with untoward responses.

Number of treatments. Most cases of DCS respond satisfactorily to a single hyperbaric treatment, although repetitive treatments (typically once daily) may be required depending on the patient's initial response. For patients with residual deficits following the initial recompression, repetitive treatments are recommended until clinical stability has been achieved. HBO_2 should be administered repetitively as long as stepwise improvement occurs, based upon clearly documented symptoms and physical findings. The need for such follow-up "tailing" treatments should be supported by documentation of the clinical evaluation before and after each treatment. Complete resolution of symptoms or lackof improvement on two consecutive treatments establishes the endpoint of treatment; typically no more than one to two treatments [27]. The optimal choice of recompression table for repetitive treatments has not been established. It is generally agreed that for tailing treatments, repetitive long treatment tables (such as the U.S. Navy Table 6) [49] are not justified, and it is typical to utilize shorter treatments (such as the U.S. Navy Table 5) [49] or even wound treatment tables conducted at 2-2.4 ATA for this purpose. Although a small minority of divers with severe neurological injury may not reach a clinical plateau until 15-20 repetitive treatments have been administered, formal statistical analysis of approximately 3,000 DCI cases supports the efficacy of no more than five to 10 repetitive treatments for most individuals [56].

Time from symptom onset to hyperbaric treatment. Available data do not convincingly demonstrate superior outcomes in "rapid" versus delayed treatment [53,57]. For example, in two published series, time to treatment greater than 2,447 or 4,846 hours was as effective as earlier treatment. However, most series in recreational diving lack cases with extremely short symptom-to-recompression latency as comparators. In contrast, there are data from military experimental diving, which suggest immediate recompression is extremely effective in controlling symptoms [43, 58-59]. As a general principle, timely treatment is preferred. Currently available data have not established a maximum time (hours or days) after which recompression is ineffective [59-65].

Monoplace chamber treatment. Monoplace chambers were originally designed for the continuous administration of 100% oxygen and were not equipped to administer air for "air breaks," which are incorporated in U.S. Navy treatment tables for DCS. For monoplace chambers of

this type, tables are available for treatment of decompressionsickness that are shorter than standard USN treatment tables [66-68]. Retrospective evidence, using telephone follow-up, suggests that such tables may be as effective as standard USN tables for the treatment of mildly or moderately affected patients [42, 69-70] However, many monoplace chambers are now fitted with the means to deliver air to the patient, and thus can be used to administer standard 2.82 ATA USN treatment tables [71].

Saturation treatment. For severe DCS in which gradual but incomplete improvement occurs during hyperbaric treatment at 60 fsw, saturation treatment may be considered if the hyperbaric facility has the capability. There is, however, no convincing evidence that such interventions are associated with a better outcome than other approaches.

In-water recompression. In-water recompression (IWR) of injured divers has been proposed as an emergency treatment modality if evacuation of a symptomatic diver to a hyperbaric facility cannot be performed in a timely manner. The advantage of IWR is that it can be initiated within a very short time after symptom onset. IWR while breathing air has been used by indigenous divers with a high reported success rate, although clinical details are scant [72]. There is anecdotal evidence that IWR using oxygen is more effective [73]. However, a major risk is an oxygen convulsion resulting in fatal drowning. IWR using oxygen has been discussed in the literature [51,73,74] and is described in the U.S. Navy Diving Manual [49]. Typical IWR oxygen-breathing protocols recommend depths no greater than 30 fsw (USN) or shallower [73]. Recommendations include a requirement that the diver not use aregular scuba mouthpiece but rather a full face mask, surface-supplied helmet breathing apparatus or regulator retention strap ("gag strap") [75]. Other requirements include the need for a tender in the water and the symptomatic diver to be tethered [73]. IWR is not recommended or may cause harm in the setting of isolated hearing loss, vertigo, respiratory distress, airway compromise, altered consciousness, extreme anxiety, hypothermia and hemodynamic instability.

In the absence of a sufficiently detailed case series from which risks and benefits can be assessed, IWR is not presently endorsed by the UHMS but was cautiously endorsed in a recent expert consensus for use by properly trained and equipped divers [51]. IWR should not be attempted without the necessary equipment, training and a full understanding of the necessary procedures.

Altitude DCS. The following algorithm has been used effectively by the U.S. Air Force [44,76].

- **Mild symptoms that clear on descent to ground level with normal neurological exam:** 100% oxygen by tightly fitted mask for a two-hour minimum; aggressive oral hydration; observe 24 hours.
- **Symptoms that persist after return to ground level or occur at ground level:** 100% oxygen; aggressive hydration; hyperbaric treatment using USN Treatment Tables 5 or 6, as appropriate. For individuals with symptoms consisting of limb pain only, which resolves during oxygen breathing while preparing for hyperbaric treatment, a 24-hour period of observation should be initiated; hyperbaric therapy may not be required.
- **Severe manifestations of DCS (neurological, "chokes," hypotension or manifestations that progress in intensity despite oxygen therapy):** continue 100% oxygen; administer intravenous hydration; initiate immediate hyperbaric therapy using USN Treatment Table 6. Recompression to 2 ATA (USAF Table 8) has also been used effectively for altitude DCS [77].

Adjunctive therapy. Adjunctive treatments such as first-aid oxygen administration, fluid resuscitation and for patients with leg immobility, venous thromboembolism prophylaxis, are indicated. These are discussed in detail in a separate monograph [78], which is available on the Undersea and Hyperbaric Society website at: (*www.uhms.org/images/Publications/ADJUNCTIVE_THERAPY_FOR_DCI.pdf*).

Evidence-based review

The use of HBO_2 for decompression sickness is an AHA level I recommendation (level of evidence C). A number of adjunctive therapies have been used for the treatment of DCS (Table 1) and discussed in the Report of the Decompression Illness Adjunctive Therapy Committee of the Undersea and Hyperbaric Medical Society [78]. These guidelines can be accessed via the internet at: *www.uhms.org/images/Publications/ADJUNCTIVE_THERAPY_FOR_DCI.pdf.*

Utilization review

Utilization review should occur after 10 treatments.

Table 1. Evidence-based review of adjunctive therapies for DCS

	CONDITION							
	AGE (no significant inert gas load)		DCS: pain only/ mild		DCS: neurological		DCS: chokes (cardiorespiratory)	
	Class	Level	Class	Level	Class	Level	Class	Level
surface O_2 (1 ATA)	I	C	I	C	I	C	I	C
intravenous fluid therapy	D5W† III LR/crystalloid‡ IIb colloid‼ IIb	C	D5W† III LR/crystalloid‡ IIb colloid‼ IIb	C	D5W† III LR/crystalloid‡ IIb colloid‼ IIb	C	D5W† III LR/crystalloid‡ IIb colloid‼ IIb	C
aspirin	IIb	C	IIb	C	IIb C		IIb	C
NSAIDs	IIb	C	IIb	B	IIb	B	IIb	C
anticoagulants*	IIb	C	III	C	IIb§	C	IIb	C
corticosteroids	III	C	III	C	III	C	III	C
lidocaine	IIa	B	III	C	IIb	C	III	C

(Table from Moon:78 www.uhms.org/images/Publications/ADJUNCTIVE_THERAPY_FOR_DCI.pdf)

§ For decompression illness with leg immobility, low molecular weight heparin is recommended as soon as possible after injury (enoxaparin 30 mg or equivalent, subcutaneously every 12 hours).

† 5% dextrose in water.

‡ Lactated Ringer's solution, normal saline or other isotonic intravenous fluid not containing glucose.

‼ Starch, gelatin or protein fraction with isotonic electrolyte concentration.

* Full dose heparin, warfarin, thrombin inhibitors, thrombolytics, IIB/IIIA antiplatelet agents.

Cost impact

Only those people exposed to increased ambient pressure (divers or compressed air workers) or who suffer decompression sickness at altitude are affected. Because there are relatively few individuals who develop this condition, the application of HBO_2 will be limited. HBO_2 is a treatment that usually provides resolution or significant improvement of this disorder that can otherwise result in permanent spinal cord, brain or peripheral nerve damage or death, and is therefore an exceptionally cost-effective treatment.

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CLINICAL CASE REPORT

Successful replantation of amputated penis with adjuvant hyperbaric oxygen therapy

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ABSTRACT

Successful penile replantations are rarely reported in the literature and are associated with significant complications. We present a case of a patient who auto-amputated his penis. Delayed microvascular replantation was performed approximately 14 hours following injury. He was treated with a phosphodiesterase inhibitor postoperatively, and adjuvant hyperbaric oxygen (HBO_2) therapy was started 58 hours after replantation; 20 treatments at 2.4 atmospheres absolute (ATA), twice daily for eight days, followed by once daily for four days. Perfusion of the replanted penis was serially assessed using fluorescent angiography. With some additional surgical procedures including a split- thickness skin graft to the shaft due to skin necrosis he has made a complete recovery with return of normal urinary and sexual function. This unusual case illustrates the potential benefit of HBO_2 therapy in preserving viability of a severed body part. Fluorescent angiography may have potential utility in monitoring efficacy of HBO_2.

INTRODUCTION

Penile amputation is a rare genitourinary tract injury. The majority of cases are the result of self-mutilation in psychiatric patients [1-3]. Though rare, successful replantation of penile amputations has been reported in the literature with and without using microvascular techniques and adjuvant treatments, but are associated with significant complications. A standardized therapeutic approach for penile replantation does not exist. Hyperbaric oxygen therapy (HBO_2) is an approved adjuvant treatment for individuals with compromised grafts and flaps and has been advocated for patients with decreased blood flow due to inadequate inflow and/or outflow.

CASE REPORT

The patient is a 22-year-old man with a history of depression and self-injury who auto-amputated his penis 2 cm from the base of the shaft using a knife. He was found by first responders approximately three hours after injury. The severed penis was located, placed in a clean plastic bag containing saline-soaked gauze and immersed in ice for transport with the patient to the hospital. The scrotum and testicles were intact. There was an adherent hematoma covering the penile stump without active bleeding.

Replantation was performed approximately 14 hours following injury. Direct primary reanastomosis of the corpora and urethra were performed first with insertion of 14-French Foley catheter across the anastomosis. Microvascular anastomosis was then done, with repair of two large-caliber deep dorsal veins using grafts harvested from the right forearm and coaptation of three dorsal nerves. There were no identifiable arteries that could be anastomosed.

Buck's fascia was repaired and primary skin closure was performed with placement of Penrose drains. Intraoperative transcutaneous Doppler studies signals were found over the repaired veins. Fluorescent angiography (indocyanine green) was also performed postoperatively using the SPY imaging system (Novadaq® Technologies Inc.) and showed no perfusion of the penis (Figure 1). However, there was active bleeding from the skin margins and oozing from the dorsal veins throughout the procedure. Active bleeding was also noted from the glans at the completion of surgery without evidence of venous congestion.

KEYWORDS: fluorescent angiography; hyperbaric oxygen; hyperbaric oxygen therapy; penis; replantation

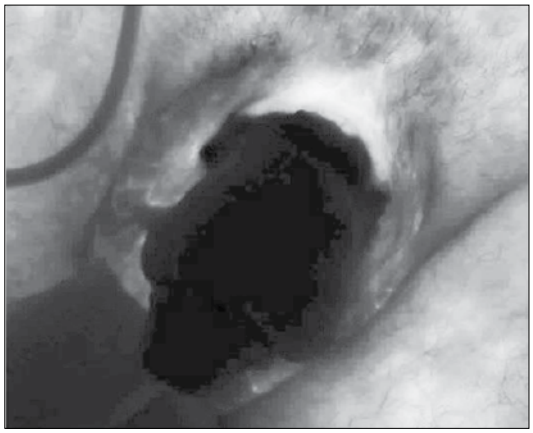

Figure 1. Postoperative fluorescent angiography performed prior to initiation of HBO_2 therapy showed no perfusion in the replanted penis distal to the anastomosis.

Figure 2. The left image shows the attached replant prior to first HBO_2 treatment. The image on the right is the appearance after the first HBO_2 session. The tissue is pinker due to hyperoxygenation. The blisters present are ischemic blisters.

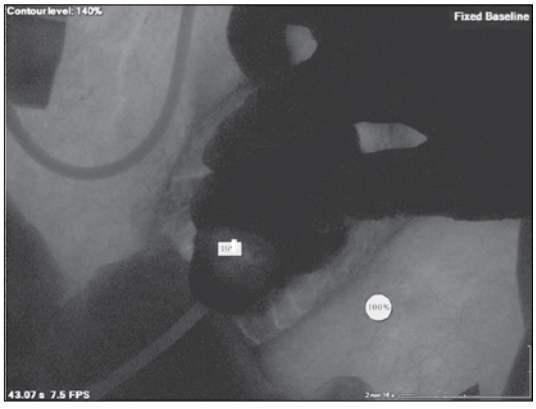

Figure 3. Fluorescent angiography after first day of HBO_2. 19% perfusion was noted in the glans compared to baseline (skin of thigh, 100%).

Figure 4. Skin necrosis of the shaft.

The patient was treated postoperatively with the phosphodiesterase inhibitor tadalafil (Cialis, registered trademark Eli Lilly and Company) at 10 mg once daily, and HBO_2 therapy. Monitoring the viability of the replanted penis was done by clinical examination. Figure 2 shows the appearance of the replant prior to and following the first HBO_2 treatment on postoperative day 2. HBO_2 was started 72 hours after amputation and 58 hours after replantation. Treatments were performed with 100% oxygen at 2.4 atmospheres absolute (ATA). The patient received a total of 20 treatments, twice daily for eight days followed by once daily for four days, until a plateau in the clinical appearance of the replant was achieved. Fluorescent angiography (SPY) was also repeated after the first day of HBO_2 treatment on postoperative day 3 (Figure 3).

Progressive reduction in swelling improvement of color was noted during the course of HBO_2 therapy. Diffuse superficial skin necrosis of the shaft developed, with formation of eschar (Figure 4).

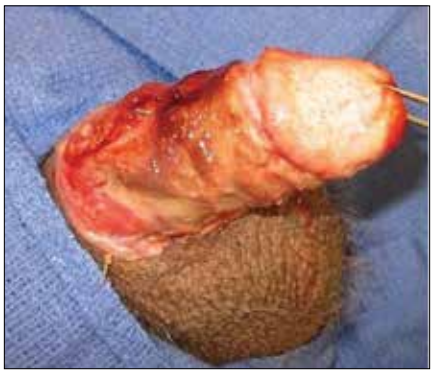

Figure 5. Debridement of necrotic skin *(above)* followed by split -thickness skin graft to the shaft of the replant *(right)*.

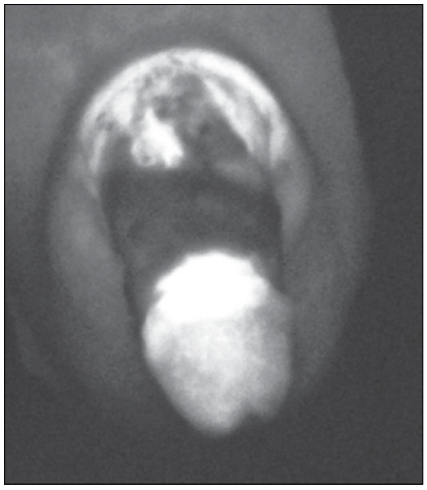

Figure 6. Fluorescent angiography after completion of HBO_2 therapy shows restoration of normal flow to the glans and base of the shaft *(left)*.

Debridement of the eschar was done 20 days after replantation and a split-thickness skin graft was performed (Figure 5). HBO_2 therapy continued after the skin graft to the shaft. A meatal stenosis also developed which was corrected. Figure 6 is an image from the fluorescent angiography study performed after completion of HBO_2 therapy.

At four months after injury, the patient was able to urinate normally, achieve an erection and ejaculate. There is partial recovery of sensation and good aesthetic result (Figure 7).

DISCUSSION

Major self-mutilation (MSM) is a rare but catastrophic complication of severe mental illness and often results in permanent loss of an organ or its function. MSM of the external genitals is also known as Klingsor syndrome [1,2]. The majority of patients are Caucasian and in their third or forth decade of life [3]. The testicles are the most commonly amputated organ, followed by the penis [3]. This patient was typical: age 23 with history of major depression and cutting. It was his first attempt at major self-mutilation.

Because penile amputation is an unusual injury, a standardized approach to management does not exist. The

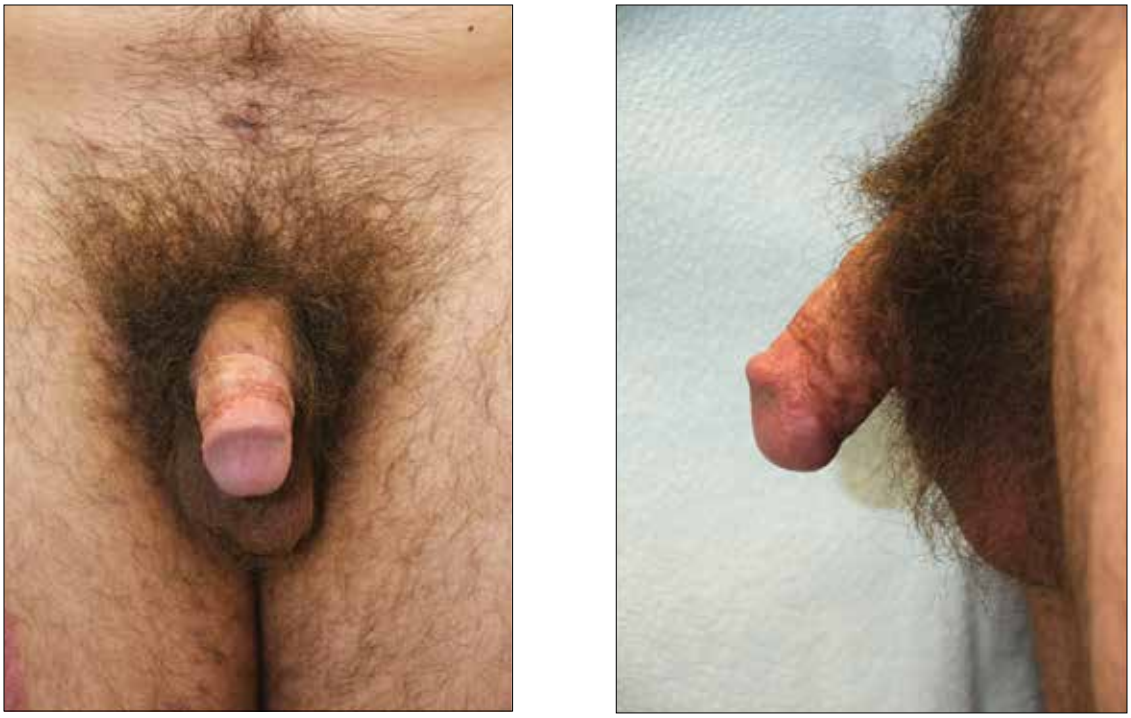

Figure 7. Appearance of replant four months after surgery.

first documented case of penile replantation was reported in 1929 by Ehrich, who realigned the penile structures without anatomizing vessels or nerves [4]. Graft survival in non-microvascular anastomosis depends on corporal sinusoidal blood flow and has been associated with significant complications, including skin necrosis (most common), fistula formation, urethral stricture, permanent loss of sensation and impotence [2, 7]. Treatment of penile amputation has been improved by application of microvascular surgical technique, which provides earlier restoration of blood flow. The first microvascular replantations were reported by Tamai, et al. and Cohen, et al. in 1977 [5, 6], with at least 30 cases of successful microvascular replantation subsequently reported in the literature.

Clinical evaluation, including observation of visual changes of skin color, is a practical component of the care for these patients. Other factors contributing to positive clinical outcome include degree of injury, type of injury and duration of ischemia. Hypothermia has been shown to prolong the ischemia time and tissue survival. The amputation should be immersed in ice without direct contact between the tissue and ice, as was done in this case [7]. Another critical factor for successful replantation appears to be the adequacy of venous outflow to reduce post-operative edema and necrosis [8, 9].

The use of non-surgical adjuvant therapies that optimize blood flow and tissue oxygenation to preserve viability has rarely been reported [10-13]. One modality employed in this case was tadalafil, 10 mg once daily. Tadalafil is a cGMP-specific phosphodiesterase type 5 inhibitor most commonly used for treatment of erectile dysfunction. In the presence of nitric oxide, tadalafil increases levels of cGMP, which results in smooth muscle relaxation and increased blood flow in the corpus cavernosum.

HBO_2 therapy was another adjuvant therapy utilized in this case. HBO_2 promotes wound healing and tissue viability through several mechanisms. In addition to increasing plasma and tissue oxygen partial pressures, HBO_2 reduces edema and effects of reperfusion injury by reducing free radical formation. Another mechanism by which HBO_2 acts is to stimulate angiogenesis. Although the HBO_2 treatment was started 72 hours after injury in this case the therapy should be started as soon as possible post injury to facilitate wound healing.

Both early intervention with HBO_2 and early referral to a multidisciplinary team will allow for more successful organ replantation. Of unique interest in this case was demonstration of progressive restoration of blood flow during HBO_2 by the technique of fluorescent angiography despite the fact that an arterial anastomosis could not be performed during surgical replantation. In cases where venous congestion is a concern, other modalities such as leech therapy can be utilized [14].

CONCLUSIONS

This unusual case illustrates the potential benefit of HBO_2 in preserving viability of a severed penis following replantation. We attribute successful healing with regain of function in this unusual case of a replantation of an auto-amputated penis to the multidisciplinary treatment approach including microvascular surgical techniques as well as adjuvant pharmacologic and HBO_2 therapies. Proposed mechanisms of HBO_2 efficacy in this case include reduced swelling and reperfusion injury, increased tissue oxygen concentration and tension as demonstrated by fluorescent angiography. Our recommendation, based on this case and the previous high incidence of complications following penile replantation with no arterial anastomosis, is the routine use of HBO_2 in cases where decreased blood flow is a concern.

HBO_2 therapy should be continued despite superficial necrosis of penile replants. Fluorescent angiography may have potential utility in monitoring efficacy of and quantifying response to HBO_2 therapy.

Conflict of interest statement

The authors have declared that no conflict of interest exists with this submission.

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CLINICAL CASE REPORT

Hyperbaric oxygen therapy for perioperative posterior ischemic optic neuropathy: a case report

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ABSTRACT

Purpose: To report the successful treatment of post-operative posterior ischemic optic neuropathy (PION) with hyperbaric oxygen therapy and to review the current literature on the pathogenesis and treatment of PION.

Observations: During an angiographic procedure at a community hospital, an elderly woman had a transient drop in blood pressure after receiving an intravenous dose of hydralazine. During recovery, the patient experienced bilateral vision loss. She was transferred to our specialty referral center for treatment with hyperbaric oxygen. We followed Table 5 in the U.S. Navy Diving Manual, the protocol for decompression sickness. Our patient's vision improved markedly immediately after the first session and continued to improve throughout the course of treatment to its completion. Follow-up ophthalmology visits found the patient's vision to be close to baseline.

Conclusions and importance: PION is a rare condition. It has been difficult to determine a successful therapeutic approach because of the lack of large case-controlled studies. Hyperbaric oxygen has been used to treat other ischemic ophthalmic conditions, but there are only few reports of its use in patients with PION. Systemic steroids and antiplatelet therapy have also been used, with mixed success. In our patient, the combination of hyperbaric oxygen therapy and steroids was successful in restoring vision after postoperative PION. ∎

KEYWORDS: case reports; hyperbaric medicine; hyperbaric oxygen therapy; ischemic optic neuropathies; ophthalmology; optic neuropathy,; post operative visual loss; posterior ischemic optic neuropathy; retinal artery occlusion; vision; visual loss

INTRODUCTION

Ischemic optic neuropathies (IONs) can be divided anatomically into anterior ischemic optic neuropathy (AION) and posterior ischemic optic neuropathy (PION) [1]. Postoperative ION is almost universally a non-arteritic ischemic optic neuropathy (NAION) caused by hemodynamic and vascular factors, as opposed to arteritic ischemic optic neuropathy, a manifestation of giant cell arteritis, a generalized inflammatory disease.

In this article we focus on postoperative NAION. Its estimated overall incidence is 2.3 to 10.2 cases per 100,000 persons older than 50 years of age [2]. PION accounts for less than 10% of all non-post-surgical ION cases [3] but for 67% of cases of postoperative visual loss (POVL) caused by ischemic neuropathies, according to a report by the American Society of Anesthesiologists [4].

Understanding the anatomy of the optic nerve helps in understanding the pathophysiology of the disease. The anterior part of the optic nerve, at the optic disc, is supplied by branches of the posterior ciliary arteries, forming the circle of Zinn-Haller [5]. The posterior part of the nerve is supplied mainly by collaterals from the ophthalmic artery, and by small branches from surrounding arteries – the anterior superior hypophyseal, the anterior cerebral, the anterior communicating, and the anterior ophthalmic arteries [6], receiving no axial supply from the central retinal artery (CRA) that runs in the center of the nerve [7, 8]. Lack of axial supply creates a watershed area in the central part of the posterior optic nerve [7, 8]. This is thought to be the reason why the most common pattern of visual field defects in PION is central, either alone or in combination with other areas of the peripheral visual field [7, 8]. Histopathologic studies have confirmed wide variation in the

the distribution of ischemia when studying cross sections of posterior optic nerves at different distances from the globe [8].

In general, NAION typically presents as acute, painless visual loss of varying degrees. Bilateral loss is more common in postoperative NAION [2]. Physical examination reveals decreased color vision, an altitudinal visual field defect, and a relative afferent pupillary defect (APD), which might be absent in bilateral PION [5]. Optic disc edema is seen only in AION (it is absent in PION). In AION, a congenitally anomalous "crowded" optic nerve is usually present in the unaffected eye, whereas both optic nerves may appear normal in PION. While AION presents with a classic altitudinal visual field defect, a central visual field defect can often be seen in PION.

Perioperative ION presents within several hours to a few days after non-ophthalmic surgery [9,10]. It has been documented most frequently after spinal surgery, radical dissections of the neck, and cardiac procedures [1,4,11]. General risk factors for NAION include hypercholesterolemia, sleep apnea syndrome, atherosclerosis, cardiovascular disease, history of stroke, tobacco use, and use of phosphodiesterase inhibitors such as sildenafil (Viagra) [5, 12]. Procedure-specific risk factors include hypovolemia, hypotensive episodes, and prone positioning [2].

Data regarding the treatment of PION and IONs, in general, are sparse and mainly come from case reports. We found no randomized control trials about the treatment of PION. The most important steps in its treatment are preventive measures and hemodynamic optimization [7, 8]. Prophylactic measures include avoiding hypotension, avoiding hemodilution, minimizing physical pressure on the eyeball, decreasing time of surgery, and limiting time of prone positioning. A few authors have suggested the use of corticosteroids for AION [3,13] but a beneficial effect of steroids for PION has not been documented. Hyperbaric oxygen (HBO_2) therapy has been found to be effective in treating non-arteritic ischemia in central retinal artery occlusion (CRAO) [14,15]. Because of the similarity in the underlying pathophysiology of CRAO and PION, hyperbaric oxygen seems to be a reasonable consideration in the therapeutic strategy for NAION. Bojić described two patients with AION who were treated with HBO_2, suggesting a beneficial outcome [16], but Arnold could see no advantage to HBO_2 treatment for his patient with that type of neuropathy [3]. We found no reports of the use of HBO_2 for the treatment of PION.

Prognosis of PION varies, with different reports predicting poor outcome of this rare disease. However, few papers predicted that early and aggressive treatment with oxygen and steroids could prevent disease progression and deterioration of vision and in some cases restoration of vision if treated early and promptly [2,7].

CASE REPORT

An 82-year-old woman with a history of hypertension, hyperlipidemia, lupus erythematosus, peripheral vein disease (PVD), and subclavian stenosis plus an ocular history of cataract excision was admitted to a community hospital to undergo angiography for the evaluation and treatment of left subclavian stenosis. The vascular surgeon at the transferring hospital reported that the patient experienced a transient drop in blood pressure during the procedure, from a systolic level of 170 to 190 mmHg to 100 mmHg. This change was attributed to administration of a single intravenous dose of hydralazine. A systolic pressure of 100 mmHg does not constitute hypotension, but we believe the drop to this level from our patient's high baseline pressure could have caused decreased perfusion and subsequent hypoxia. Immediately after the procedure, in the recovery unit, the patient complained of profound bilateral vision loss. Her visual acuity was found to be hand motion in both eyes (OU). She had no other focal findings except mild confusion. Emergent consultations from the ophthalmology and neurology teams were obtained. The patient's funduscopic exam was normal. Immediate computed tomography (CT) and magnetic resonance imaging (MRI) studies showed no signs of infarction, hemorrhage, or mass. CT angiography of her head and neck showed patent carotids, with less than 50% occlusion, and normal posterior circulation of the brain. An emergent echocardiogram obtained at the transferring hospital showed an ejection fraction of 60%, with grade 1 diastolic dysfunction. The diagnosis of exclusion was PION. After a phone consultation with the on-call hyperbaric medicine physician, the patient was accepted for transfer to our specialty referral center for emergent HBO_2 therapy.

After we examined the patient, we chose to follow our institutional protocol for CRAO, acknowledging that the mechanism of injury and the rationale for the use of hyperbaric oxygen for that condition and PION are different [15]. The specific treatment table was selected at the bedside based on clinical judgment in an attempt to maximize salvage of the patient's vision. For compression, we followed the algorithm in Table 5 of the U.S.

Navy Diving Manual [17], designed to treat decompression illness. In this algorithm, patients are compressed at a rate of no more than 20 feet/minute until they reach a depth of 2.8 atmospheres absolute (ATA). Upon reaching that depth patients begin two 20-minute intervals of breathing 100% oxygen, with a five-minute air break between them. Patients are then decompressed slowly at a maximum rate of 1 foot/minute until they reach 2.0 ATA. Once they reach that depth, they take a five-minute air break before breathing 100% oxygen for an additional 20 minutes. This is followed by a five-minute air break and then ascend to surface. Total treatment time is 135 minutes.

When the patient arrived at our facility, her examination findings were similar to those stated above, with a visual acuity of hand motion OU (Table 1). It was difficult to perform a full slit-lamp examination (SLE) or a direct funduscopic examination because of the patient's altered mental status. After obtaining consent from the family, the patient was taken for an initial HBO_2 treatment. Concurrently, she was started on intravenous (IV) methylprednisolone, 1 g/day, with the hope of achieving a synergistic effect with HBO_2 therapy, as has been reported for optic nerve injuries [1].

After the first treatment the patient's vision showed immediate improvement, with visual acuity reaching 20/40 OU. Unfortunately, VA exam after the first dive was not documented. Another HBO_2 treatment was administered on the morning of the second day (2.0 ATA for 120 minutes). Repeat ophthalmological examination (Table 1) performed by an attending ophthalmology physician revealed the following in visual acuity :

- right eye (oculus dexter/OD) 20/40;
- left eye (oculus sinister/OS) 20/40+2, showing no improvement with pinhole.

Her pupils were briskly reactive without APD. Maculas were flat, with mild retinal pigment mottling, but no cherry-red spot or edema. Retinal vessels were attenuated in both eyes.

The patient's third and final hyperbaric oxygen session was administered later on the second day of admission. It lasted for 120 minutes at 2.4 ATA. The patient's vision continued to improve after the second and third sessions and approximated her baseline acuity (Table 1). A final ophthalmologic evaluation revealed visual acuity of 20/20 in both eyes, briskly reactive pupils without APD, improvement on Ishihara color plate detection (now 7 of 11 images identified with both eyes), and no color desaturation.

Because of the marked improvement in the patient's vision, HBO_2 was stopped after the third session and she was discharged home, with a scheduled follow-up appointment at a neuro-ophthalmology clinic. At follow-up one week after discharge, examination showed an improvement in visual acuity (Table I). At a second follow-up appointment within a month after discharge the patient's visual acuity was 20/40+2 in her right eye and 20/30 on the left, with no new findings. Her vision returned to levels comparable to baseline and remained there one month after completion of treatment.

DISCUSSION

Treatment of PION is not well studied and documented, mainly because of the low incidence of the disease. To know what treatment options are beneficial we need to understand its underlying pathophysiology. The posterior part of the optic nerve has a very complex system of blood supply, with collaterals from multiple major arteries (Figure 1). Because of this intricate blood supply, the posterior segment is hypothesized to contain watershed areas, making the posterior segment of the optic nerve prone to hypoperfusion and ischemia [7, 8].

A variety of factors can affect optic nerve perfusion: arterial autoregulation; venous stasis; increased intraocular pressure during surgery, caused by orbital edema or mechanical pressure on the eye; and decreased arterial perfusion related to transient hypotension, hemodilution, or blood loss [1, 11, 18]. Because of the lack of adequate histopathologic evidence, it is difficult to determine if perioperative PION is caused mainly by an arterial or a venous insult [11]. In either case, the underlying pathophysiology of PION is thought to be ischemic in nature [2] and would naturally follow the ischemia and reperfusion (IR) injury pattern.

The first recommended line of treatment of PION is the identification of risk factors and the prevention of intraoperative events that might lead to this condition. Those events include any drop in blood pressure during surgery, hypovolemia, and prolonged surgeries that might cause edema to the optic nerve, especially in the prone position. In our case, we suspect that the drop in blood pressure from the patient's baseline level to 100 mmHg, although considered normal for other patients, led to a decrease in blood flow to the posterior optic nerve area.

Once loss of vision has occurred and is detected, immediate treatment with high-flow oxygen is warranted, given that the differential diagnosis for sudden-onset visual loss includes vision-threatening disorders such

Table 1. Summary of ophthalmologic exam findings during the treatment course

	Initial Exam	**After Second HBO_2 Treatment**	**After Third HBO_2 Treatment**	**One Week After discharge**	**One Month** After Discharge
Visual acuity	Hand motion OU	OD: 20/40, no improvement with pinhole OS: 20/40+2, no improvement with pinhole	20/20 OU OS: 20/30	20/25 OU	OD: 20/40+2
Extraocular movement		Full OU	Full OU	Full OU	Full OU Full OU
Alignment	–	Ortho in primary gaze	Ortho in primary gaze	Ortho in primary gaze	Ortho in primary gaze
Pupils	–	2.5 to 1.5 and brisk OU	3 to 2 and and brisk OU	Equally round, reactive to light	Equally round, reactive to light
Afferent pupillary defect	–	Not present OU	Not present OU	Not present OU	Not present OU
Tonometry	–	–	–	20 OU	OD 20 OS 21
Ishihara test	–	OD: 5/11 OS: 1/11	7/11 OU	–	-
Color desaturation	–	OD: 50%	None	–	-
SLIT LAMP/PENLIGHT EXAM					
External/lids	-	Lashes dry Periorbital skin OU Poliosis OU	Lashes dry Periorbital skin OU Poliosis OU	Brow ptosis OU Dermatochalasis of upper lids	Normal OU
Conjunctiva/sclera	–	White and quiet OU	White and quiet OU	Injected OU	White and quiet OU
Cornea	–	Clear/arcus OU	Clear/arcus OU	Clear OU	Clear OU
Anterior chamber	–	Deep and quiet OU	Deep and quiet OU	Deep and quiet OU	Deep and quiet OU
Iris	–	Regular, round, reactive OU	Regular, round, reactive OU	Regular, round, reactive OU	Regular, round, reactive OU
Lens	–	Posterior chamber intraocular lens OU	Posterior chamber intraocular lens OU	Posterior chamber intraocular lens OU	Posterior chamber intraocular lens OU
Vitreous	–	–	–	Clear OU	-
DILATED FUNDUS EXAM					
Disc	–	Sharp margins OU Mild PPA OS>OD No pallor or disc edema OU	-	Disc without pallor OU	-
Cup/desk ratio	–	–	–	0.35 without pallor OU	-
Macula	–	Flat/pigmentary mottling OU	–	Decreased foveal reflex OU	-
Vessels	–	Attenuated OU	–	Arterial attenuation OU	-
Periphery	–	No holes/tears/intraretinal hemorrhage/CWS OU	–	No holes or tears OU	-

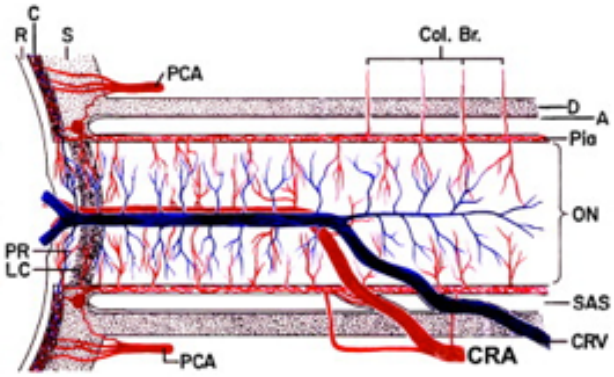

Figure 1: Optic nerve blood supply.
A, arachnoid; C, choroid; CRA, central retinal artery; Col. Br., collateral branches; CRV, central retinal vein; D, dura; LC, lamina cribrosa; ON, optic nerve; P, pia; PCA, posterior ciliary artery; PR, prelaminar region; R, retina; S, sclera; SAS, subarachnoid space. (Used with permission from Hayreh 2009 [8]).

as CRAO. Whenever CRAO is suspected, it is standard to treat patients immediately with normobaric oxygen. Murphy-Lavoie and colleagues [15] recommended treating suspected CRAO patients immediately with high-flow oxygen while waiting for HBO_2 therapy. Butler and associates [21] also suggested that, due to the time sensitivity of this disease and its sequelae, any patient presenting with sudden vision loss and suspected CRAO should be started immediately on high-flow oxygen and then HBO_2 if the symptoms do not resolve. They found that the response to treatment was best when treatment was started within 24 hours after the onset of symptoms. They categorized PION as one of the entities that can benefit from HBO_2 due to the similarities in the pathophysiologic processes of PION and CRAO.

HBO_2 for CRAO is part of the treatment recommended by the Hyperbaric Committee of the Undersea and Hyperbaric Medical Society (UHMS) [21]. In some studies, it was effective therapy for CRAO when initiated early [15, 22-25]. Due to its importance, HBO_2 was considered by the American Heart Association to be effective therapy, with a level IIb evidence for efficacy [15]. In a retrospective chart review, HBO_2 was most beneficial when initiated within eight hours after the onset of CRAO symptoms and showed varying degrees of success when initiated later than eight hours after onset [22]. Nonetheless, patients should be considered for HBO_2 if they present within 24 hours after symptom onset, as some reports showed some benefit when treated within this period [15].

No large-scale studies have been conducted to test the true effect of HBO_2 on the resolution of PION, especially when it is treated early, and we found no reports of hyperbaric oxygen used specifically as a treatment for postoperative PION. Case reports on the use of HBO_2 for other NAIONs vary in their results. Bojić, et al. [16] concluded that HBO_2 was successful in the resolution of AION in two patients who did not respond to prednisone therapy alone. Beran and colleagues suggested that treatment of ION consist of early detection and reversal of causes but did not mention hyperbaric oxygen as a treatment; however, they did recommend it as a treatment for CRAO [26]. Kitaba and colleagues [18] suggested HBO_2 for perioperative PION. Grover and coworkers [10] suggested HBO_2 therapy for IONs but commented that its efficacy is not proven. Arnold, et al. [3], on the other hand, saw no benefit of the treatment. However, it is important to mention that timing is essential for therapy. Butler and associates [21] suggested that the unfavorable result in Arnold's observation might have been due to delay in treatment and that earlier treatment (within 72 hours after onset) would give more favorable results. Several clinical review articles expressed skepticism toward the use of hyperbaric oxygen for ocular ischemic events based on its lack of sustainable effect [3, 12, 15]. Most patients improve while being actively treated but then revert to their initial visual loss immediately afterward. Those articles, however, did not address the importance of early initiation of treatment and follow-up care.

On a molecular level ischemia triggers a complex cascade on the cellular level. Its main effect is adhesion of polymorphonuclear cells (PMNs) to the surrounding endothelial cells (ECs) through activation of cell adhesion molecules (CAMs) and other factors [19]. CAMs also cause PMNs to migrate distally along the vascular wall through diapedesis [19]. On a nuclear level ischemia affects injured cells directly and their adjacent cells indirectly by promoting apoptosis through the regulation of gene expression. Cell injury has a direct effect on the proapoptotic protein bax. Upregulation of bax leads to an increase in the expression of caspase-3 and other caspases, resulting in full activation of the apoptosis cascade and, eventually, cell death. This pattern has been found in retinal ganglionic cell layers after IR injury in humans and rats [20].

It has been proposed that hyperbaric oxygen reduces the adhesion of PMNs to injured endothelium by increasing the partial oxygen pressure and decreasing the PMN adhesion process by enhancing the release of nitric oxide (NO) [19]. Subsequently, NO prevents PMN adhesion to ECs by suppressing the intracellular expression of P-selectin and other CAMs [19]. On the other hand, HBO_2 is significantly related to the downregulation of proapoptosis proteins (bax and Caspase-3) and upregulation of anti-apoptotic proteins (bcl-2 and bcl-xL) in ischemic tissues, making it a candidate for treatment of diseases such as CRAO and ION [27].

Given the similarities in the pathophysiologic process between CRAO and ION and the evidence of success in treatment of CRAO with hyperbaric oxygen both clinically and on the cellular and nuclear levels, we presume that the hyperbaric oxygen protocol used for CRAO will have beneficial effects on patients with ION. This approach is supported by Butler and colleagues in their extensive review of the use of HBO_2 therapy in perioperative visual loss cases [21]. They recommend early oxygen administration and HBO_2 for patients with acute visual loss, in whom CRAO and IONs are part of the differential diagnosis. In our patient, application of the CRAO protocol in conjunction with intravenous administration of steroids was effective in the treatment of PION, resulting in a clinically significant and sustained recovery of vision. This successful outcome suggests that treatment protocols should be reconsidered to achieve more consistent responses.

CONCLUSIONS

Initiation of HBO_2 therapy within a few hours after the onset of PION symptoms could be beneficial in saving patients' vision. Medical treatment might be necessary to produce a sustained effect. Additional studies should be conducted to test this approach.

Conflict of interest statement

The authors have declared that no conflict of interest exists with this submission.

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CLINICAL CASE REPORT

Acute direct traumatic optic neuropathy treated with steroids, minocycline and hyperbaric oxygen: a case report

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ABSTRACT

We describe the emergency management of a man who experienced acute vision loss diagnosed as direct traumatic optic neuropathy (TON) in his right eye (no light perception) after falling from a height. TON is caused by a high-impact mechanism of injury. Clinical findings include acute vision loss, which is typically immediate, afferent pupillary defect, decreased color vision, and visual field defects. Treatment is controversial because of the lack of strong evidence supporting intervention over observation. In this case report, our treatment strategy comprised immediate hyperbaric oxygen (HBO_2) and daily high doses of a steroid. On the second day, minocycline was added to the treatment regimen for its neuroprotective effects. The patient was discharged after receiving six HBO_2 treatments and six days of intravenous solumedrol transitioned to oral prednisone. After the third HBO_2 treatment, his vision improved to 20/100; after the fourth treatment, it was 20/40 and plateaued. At the time of discharge, it was 20/40. At two-month follow-up, his corrected visual acuity was 20/60+2 in the affected eye. Immediate HBO_2 for ischemic and mechanical injury to the optic nerve following trauma is a therapeutic option.

INTRODUCTION

Traumatic optic neuropathy (TON) is a potentially blinding condition that results from a high-energy impact. The most frequent mechanism is motor vehicle collision, particularly crashes involving motorcycle drivers [1]. In a recent large retrospective study, the prevalence of vision loss after facial trauma was 0.3% [2]. TON is typically described as indirect (caused by shearing force) or direct (caused by compression by a bone fragment or foreign body). The clinical finding associated with TON is vision loss, which is usually immediate after injury in direct TON and can progress in delayed fashion in indirect TON. On exam, afferent pupillary defect (APD), decreased color vision, and visual field defects that localize to the optic nerve, commonly with altitudinal defects, will be present.

Half of patients with indirect TON recover some amount of vision spontaneously [3, 4]. Optic nerve exam with fundoscopy is typically normal at presentation because most injuries occur posterior to the globe, at the optic canal. Optic atrophy or pallor often emerges in the months following injury.

Treatment for TON is controversial due to a lack of strong evidence to support intervention over observation [5]. Although there is anecdotal evidence of improvement of direct and indirect TON cases with hyperbaric oxygen (HBO_2) therapy, few case reports about this treatment modality have been published [6, 7]. We report a positive response to emergency HBO_2 combined with medical treatment in a patient with direct TON.

CASE REPORT

A 27-year-old man with no significant past medical or ocular history was transported to a trauma center after falling 20 feet from a ladder, with resultant loss of consciousness. Unarousable for 10 minutes, he regained consciousness with amnesia for the event and right-sided headache. In addition to orthopedic injuries, primary and secondary surveys revealed a non-displaced right orbital floor fracture and an orbital roof fracture that extended to the right optic canal (Figure 1). A skull base fracture was also noted, encompassing the middle cranial fossa through the sphenoid body and lesser wing of the sphenoid. Globes appeared intact both clinically and

KEYWORDS: ocular trauma; acute vision loss; hyperbaric oxygen therapy; ophthalmologic trauma

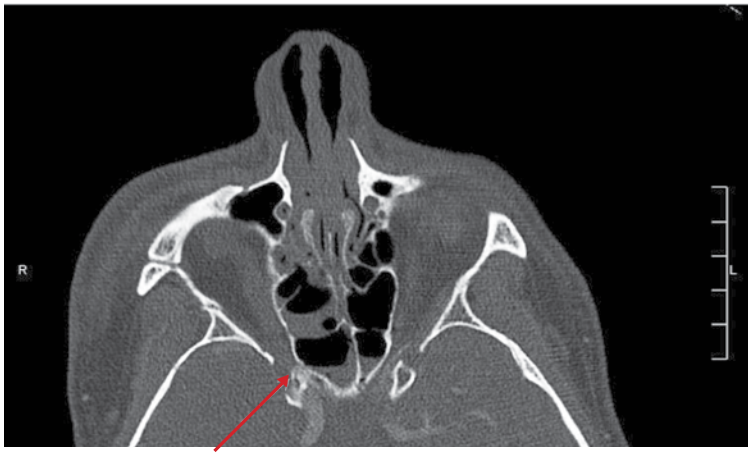

FIGURE 1: Axial computed tomography scan showing fracture of the right optic canal (red arrow).

radiologically. There were no other intracranial findings. The patient did not have eye pain or pain on eye movement, flashes, or floaters, but he described total loss of vision on the right. Initial ophthalmic examination revealed no light perception vision in the right eye, a 4.5-mm non-reactive pupil with 3+ APD, normal intraocular pressure, full motility, mild right periorbital edema and ecchymosis, and a grossly normal anterior segment and dilated fundoscopic examination. He had 20/20 vision in his left eye.

Given the severity of the TON, the morbidity associated with no light perception, and the patient's young age, we initiated high-dose steroid therapy with solumedrol, 1 gm intravenously daily, and HBO_2 therapy. The patient was treated emergently according to U.S. Navy Dive Table 5 (our institution's protocol for central retinal artery occlusion) on the day of presentation within six hours of presentation. We treated him quickly because the nervous system tissue was at risk and we were concerned about permanent damage to his vision.

On day two, the patient received two HBO_2 treatments at 2.4 ATA for 90 minutes. After the third treatment, his vision had improved significantly to 20/100 on the right with a 1+ APD and associated inferior hemifield defect with markedly diminished color saturation and brightness. He was treated with three additional daily HBO_2 sessions (2.4 ATA for 90 minutes) and daily high-dose steroids.

The patient's vision continued to improve, with the improvement plateauing to 20/40 after the fourth treatment. On treatment day two, we began administration of minocycline, 100 mg orally twice daily for its potential neuroprotective effects [7]. The patient was discharged after receiving six HBO_2 treatments and six days of solumedrol (1 gm IV) that was transitioned to oral prednisone (1 mg/kg) and tapered appropriately.

At his 2-month clinic follow-up, the patient's best corrected visual acuity was 20/60+2 on the right. Humphrey visual field testing confirmed a dense inferior hemifield defect (Figure 2). Optical coherence tomography and retinal nerve fiber layer analysis indicated significant thinning of the temporal quadrant and mild superior quadrant thinning (Figure 3).

DISCUSSION

HBO_2 therapy use in ophthalmology has generally been confined to the treatment of ischemic injury from central retinal artery occlusion and radiation retinopathy; however, there are limited case reports on its use in humans in the treatment of direct TON [8, 9]. Researchers have proposed that the mechanism of HBO_2 might be based on its neuroprotective effects against hypoxic or ischemic insults by down-regulating pro-apoptotic factors and up-regulating endogenous antioxidative enzymes and brain-derived neurotropic factors, resulting in ischemic tolerance. Using animal models of optic nerve crush injuries, investigators have shown reduction of retinal ganglion cell loss and decreased pro-apoptotic gene expression with use of HBO_2 [7, 10].

The current report features concurrent use of HBO_2 and additional medical treatments with steroids and minocycline. Steroid treatment for optic neuropathies has been widely studied but remains controversial. The significant risks of steroids are well known and include decreased immunity, poor glycemic control, and ulcerative gastrointestinal disease. Given our patient's profound vision loss on presentation, the lack of additional systemic injuries, and younger age, we concluded that steroid benefit was greater than the risk of medication complications.

In addition, we chose to use minocycline to optimize the care of this otherwise healthy patient. Minocycline is a tetracycline antibiotic with a few unique features. It is a broad-spectrum antimicrobial, with anti-inflammatory properties, excellent tissue distribution, and the ability to enter the central nervous system. It has been studied for its positive effects on microgli-

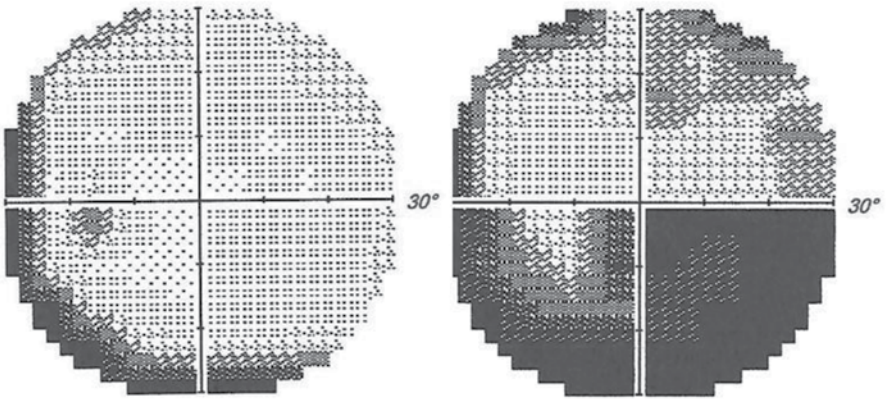

FIGURE 2: Humphrey visual fields, 30-2, obtained two months after injury (by convention, with the left eye field presented on the left). Demonstrates a rim artifact in each eye and an inferior altitudinal defect of the right eye.

Acknowledgment: Photography courtesy of Karen Klima, COT.

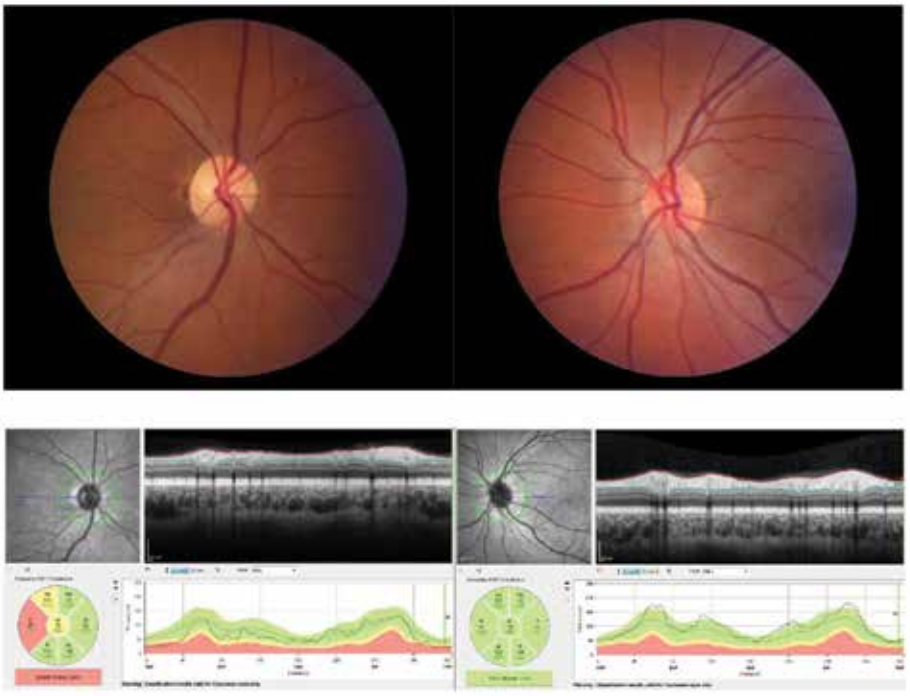

FIGURE 3: Optic nerves and optical coherence tomography of the retinal nerve fiber layer two months after injury. These images demonstrate pallor of the right optic nerve and thinning of the nerve fiber layer in the right eye.

al activation, matrix metalloproteinases, nitric oxide production, and apoptosis. It has shown neuroprotective effects in rodent models of spinal cord injury, stroke, multiple sclerosis, and Parkinson's disease. Minocycline effects have been studied in ophthalmic diseases, including retinitis pigmentosa and retinal vein occlusion [11-13]. The risks and benefits of each intervention were discussed with our patient, and he elected to proceed.

LIMITATIONS

Much of our management of this patient was based on our prior experience with acute conditions affecting the optic nerve. We treated him quickly because of the risk of ischemia to the optic nerve and vision loss. The addition of minocycline and steroids was suggested by the neuro-ophthalmology consultant because of animal studies of its neuroprotective effects. There are no large human studies that support this practice. Although unlikely because of the direct traumatic event, it is possible that the patient's vision would have improved spontaneously.

CONCLUSION

While there is no accepted standardized treatment protocol for TON, and as the use of high-dose steroids and optic nerve decompression is considered controversial in some instances, we believe that emergently treating patients with HBO_2 for ischemic and mechanical injury to the optic nerve following trauma is an under-studied and under-utilized therapeutic option that deserves further investigation.

Conflict of interest statement
The authors have declared that no conflict of interest exists with this submission.

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CLINICAL CASE REPORT

Hyperbaric oxygen therapy in the treatment of malign edema complication after arteriovenous malformation radiosurgery

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ABSTRACT

A 16-year-old female patient with headache was admitted to our hospital. Radiological examination showed a Spetzler-Martin Grade III arteriovenous malformation (AVM) located at the left frontal lobe. Volume-staged stereotactic radiosurgery (SRS) treatment performed in two fractions at three-month intervals and post-procedural period were uneventful. Eight months later the patient was admitted to our hospital with headache, vomiting, right-sided facial palsy and right upper extremity paresthesia. Radiological examination demonstrated severe vasogenic edema in the left centrum semiovale and temporal region. Due to severe and steroid-resistant malign edema, hyperbaric oxygen (HBO_2) therapy was performed as an alternative treatment option. Neurological symptoms resolved completely after HBO_2. Radiological examination demonstrated serious improvement of brain edema and mass effect.

INTRODUCTION

Cerebral arteriovenous malformation (AVM) is a congenital vascular anomaly that consists of a vessel tangle, resulting in and causes direct blood flow from arterial input to the venous system without an intervening capillary network to decrease the pressure. The most important risk is the rupture of the AVM, which has 10% mortality and 30%-50% morbidity from each bleed [1]

Microsurgical resection, endovascular occlusion, stereotactic radiosurgery (SRS), or combinations of these therapies are the main treatment options for these lesions. The morbidity and mortality risk of microsurgical treatment is higher especially for deep AVMs and/or AVMs in eloquent areas. For these types of AVMs gamma knife radiosurgery may be the most appropriate treatment option.

Although SRS allows giving an appropriate dose to a confined target area and reduces the undesired effects of radiation on normal brain parenchyma, big lesions have an increased risk of radiation injury due to high radiation doses. Early toxic effect of radiation due to SRS is rare: Seizure is the most common finding. Radiation-induced brain edema is a late onset SRS complication which is due to white matter injury (WMI) and radiologically defined as hyperintensity around target tissue on T2-weighted and FLAİR magnetic resonance imagining (MRI) [2-4].

Radiation-induced brain edema is a well-known complication after SRS for AVM. However, it is difficult to estimate which AVM patients who are treated with SRS will manifest with brain edema. Cohen-Inbar, et al. showed that 22.9% of patients whose AVMs were treated with SRS have symptomatic radiation-induced adverse effects. [5]. Most symptomatic radiation-induced brain edema can be resolved by medical treatment. Medical treatment options are steroids, anticoagulation, barbiturates and hypothermia. Surgical decompression remains a treatment option for severe and medically refractive brain edema after SRS. Hyperbaric oxygen therapy is an alternative treatment option for this type of malign brain edema complications of SRS [6].

KEYWORDS: arteriovenous malformation; brain edema, gamma knife radiosurgery; hyperbaric oxygen therapy; brain edema; neurosurgery

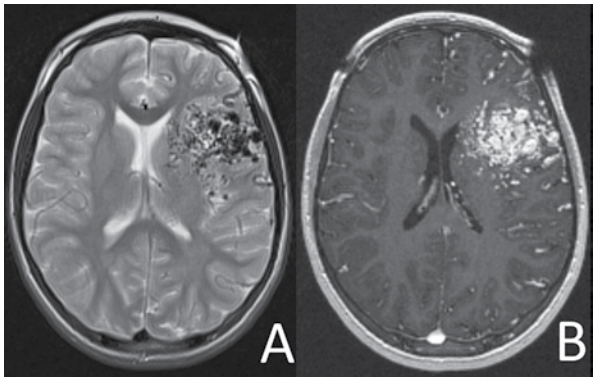

FIGURE 1: (**A**) T2-weighted axial and (**B**) T1-weighted axial contrast enhancing images of the MRI show a vascular lesion located at left frontal lobe which is compatible with AVM.

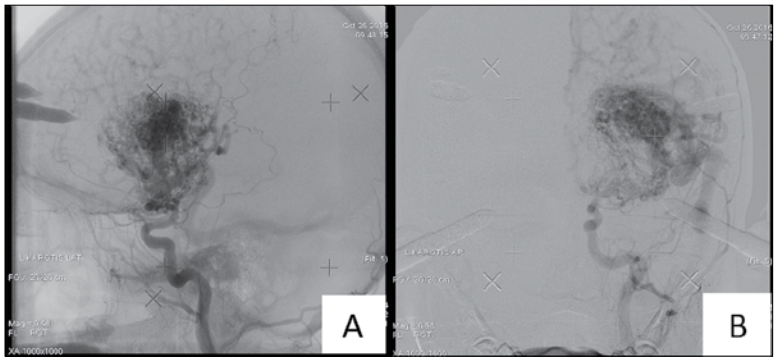

FIGURE 2: Angiography performed before SRS. (**A**) Lateral and (**B**) anteroposterior images show an AVM. Nidusis 3.5 cm in diameter. Lesion has deep venous drainage. AVM feeds from left anterior cerebral, middle cerebral and lenticulostriate arteries. Venous drainage is toward superior sagittal and transverse sinuses.

CASE REPORT

A 16-year-old female patient complained of continuous headache. It was especially problematic on the left side and had occurred over a one-year period. Neurological examination was normal. MRI revealed a Spetzler-Martin Grade III AVM located at the left frontal lobe. Angiographic examination was performed. It showed that the nidus was 3.5 cm in diameter, and the AVM had deep venous drainage. The AVM was feeding from the left anterior cerebral, middle cerebral and lenticulostriate arteries, and venous drainage was toward the superior sagittal and transverse sinuses (Figures 1, 2). Treatment options, their success rate, and possible complications were explained to the patient and her parents. It was decided that the lesion would be treated by volume-staged SRS in two fractions.

Our treatment methodology was previously described [7]. Briefly, after placement of the stereotactic head frame, MRI and angiography were performed as part of the treatment plan. The treatment plan was arranged by a neurosurgeon, a radiation oncologist and a medical physicist. SRS treatment was performed by using a Leksell Gamma Knife® Perfexion™ procedure at Gazi University Gamma Knife Center. In stage I of the radiosurgery, 12.2 cm^3 of volume was treated with a marginal dose of 18 Gy (minimum 1.7 Gy – maximum 36.6 Gy) and in stage II 13.9 cm^3 of volume was treated with a marginal dose of 18 Gy (minimum 15.1 Gy – maximum 36.6 Gy). Post procedural period was uneventful, without any symptom or complication after both sessions of SRS. The patient was treated with a prophylactic oral steroid (dexamethasone; 4 mg every six hours tapered in one week) for brain

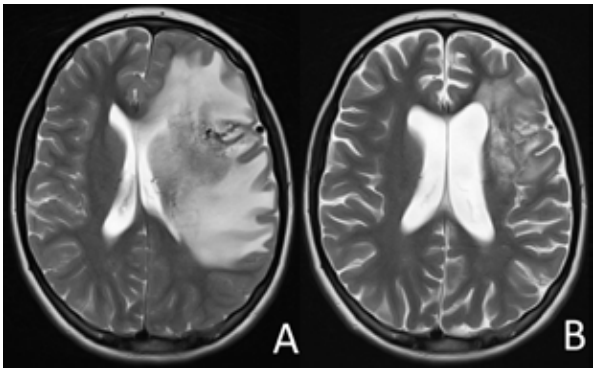

FIGURE 3: **(A)** Pre-HBO_2 T2-weighted axial MRI indicates massive brain edema which is causing midline shift. **(B)** After three months of 10 sessions HBO_2 therapy a dramatic reduction in edema on T2-weighted axial MRI is shown.

edema and non-steroidal anti-inflammatory medication (paracetamol 500 mg every eight hours) for pain control.

There was no symptom or complaint after the second session of SR. However, after eight-months the patient presented with headache, vomiting, right-sided facial palsy and right upper extremity paresthesia. Neurological examination showed House-Brackmann Grade II facial palsy on the right side. A computerized tomography (CT) of the head demonstrated severe vasogenic edema in the left centrum semiovale and temporal region. Malign edema was causing an 8 mm midline shift as well (Figure 3A). Medical treatment for edema was started with intravenous steroid (dexamethasone 6 mg every four hours). Although headache and vomiting symptoms were relieved after medical treatment, facial palsy and radiological malign edema findings persisted. Due to these persistent neurological symptoms HBO_2 therapy was agreed upon by the neurosurgeon, radiation oncologist and hyperbaric medicine specialist.

The patient was treated in a multiplace hyperbaric chamber with daily two-hour HBO_2 sessions at 2.4 atmospheres absolute, which continued for 10 days. During the 10th session of HBO_2 the patient had a new-onset generalized tonic clonic seizure, so treatment was terminated. Neurological symptoms had totally resolved after HBO_2 therapy. An MRI scan performed three months after the treatment demonstrated serious improvement of brain edema and mass effect (Figures 3B, 4).

DISCUSSION

Although SRS is an effective treatment option for AVM, it contains several complication risks. Acute onset toxic effect of radiation is rare after SRS treatment, late onset radiation-induced brain edema is a more common complication of SRS.

Radiation-induced brain edema is due to WMI and radiologically defined as hyperintensity around target tissue on T2-weighted and FLAİR magnetic resonance imagining. Different studies have shown that radiological findings of radiation-induced changes have been associated with a larger treatment dose than 12 Gy. Flickinger, et al. reported rates of 42.4% radiological findings and 10% neurological findings after SRS was associated with more than 12-Gy treatment volumes of 56.5 cm^3 [8]. Another study showed an incidence of delayed onset or progressive brain edema of 10% (four of 40 cases) after SRS for cranial metastases [9]. White matter injury and brain edema complication after SRS were observed more frequently for AVMs than for cranial metastases [2, 3].

Late-onset radionecrosis may contribute to chronic inflammatory reaction and induce cerebral edema. Corticosteroids are classical treatment options for cerebral edema in prophylaxis and for refractory cases as well. Also, new investigations are studying anticoagulation, growth factors and stem cells for treatment and prevention of radiation-induced neurotoxicity [10].

Different studies have described radiation-induced brain edema complication in 3% to 45% of patients after SRS for AVMs [11-14]. A permanent deficit has been de-

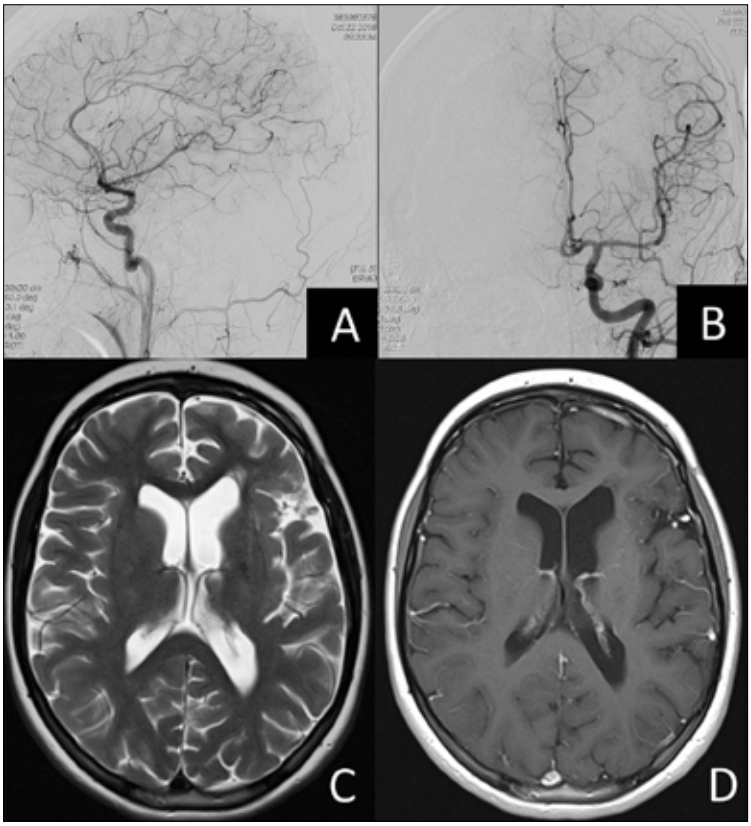

FIGURE 4: Last radiological follow-up has been performed after 48 months. **(A)** Lateral and **(B)** anteroposterior angiographic images indicate complete obliteration of the AVM. **(C)** T2-weighted axial and **(D)** T1-weighted axial contrast enhancing MRI images indicates complete resolution of edema.

scribed in 2% to 5%. Major etiological factors of edema include vasogenic edema and metabolic suppression. High radiation doses are usually the cause for this complication. Some studies are suggesting that obstruction of the draining vein is the underlying mechanism of SRS-induced edema [6].

HBO_2 therapy is a functional treatment for SRS-induced brain edema. Increasing tissue oxygenation by HBO_2 can induce cellular and vascular regeneration. HBO_2 creates oxygen level differences between radiated and non-irradiated tissue. This gradient causes a stimulus for fibroblast and capillary angiogenesis. HBO_2 can cause a decrease of lactate level in cerebrospinal fluid (CSF). This effect of HBO_2 can restore anaerobic condition of neurons [6].

HBO_2 has been used for bone and soft-tissue radionecrosis of the head and neck region [15]. HBO_2 promotes neovascularization at hypoperfused tissue. Neovascularization may cause improvement of functionality in radiation-induced damaged tissue. The main results of HBO_2 are to decrease cerebral edema, provide normal water content to the brain parenchyma, decrease severity of brain infarction, provide blood-brain barrier integrity, maintain antioxidant defenses, decrease the proliferation of foam cells and macrophages, and block astrocyte and macrophage release of neurotoxic factors. These changes cause improvement of neuronal integrity and patient outcome for patients with radiation-induced SRS [16].

Another potential treatment mechanism of HBO_2 is cerebral vasoconstriction. Cerebral vasoconstriction results in decreased cerebral blood flow. HBO_2 can also decrease vascular permeability, which in turn can decrease cerebral edema after SRS. HBO_2 may be a potential treatment option for SRS-induced brain edema with these mechanisms [6].

WMI is more frequent after SRS for AVMs and more benign lesions [17] than metastatic brain tumors. Therefore, prophylactic HBO_2 could be an option before or after SRS for AVMs [17].

CONCLUSION

Radionecrosis and brain edema are well-known complications after stereotactic radiosurgery. This complication is more frequent after treatment of arteriovenous malformation and benign tumors. Medical treatment is sufficient for most symptomatic radiation-induced brain edema, but in refractory cases hyperbaric oxygen therapy is an alternative treatment option for malign brain edema complications of SRS.

Conflict of interest statement
The authors have declared that no conflict of interest exists with this submission.

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CLINICAL CASE REPORT

Toxic inoculation associated with a presumptive stingray injury

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ABSTRACT

Introduction: Stingray spine injuries are among the most common marine animal injuries in humans. While most resolve with immersion in warm water, a few become infected and require antibiotics. We present a case report of a presumptive stingray injury that evolved to a major slough and which required prolonged healing in a patient with diabetes mellitus. Our literature review was unable to find a similarly reported case.

Materials: A co-author was asked to evaluate and manage an ominous-appearing wound on the right foot of a diabetic. The problem developed after the individual had been wading in shallow ocean beach water. The patient's diabetic sensory neuropathy obscured the immediate association of the problem with a stingray injury, but this became the presumptive diagnosis when pain developed and necessitated that he seek medical care.

Findings/Clinical Course: After an initial urgent care visit, increasing pain and worsening appearance of the patient's foot necessitated a visit to our emergency department. The patient was admitted the next day due to symptoms of systemic sepsis. On the fourth hospital day, a large bulla on the lateral side of the right foot was excised. This unroofed a full-thickness slough to the periosteum level of the underlying bones. Not until the 16th hospital day had enough improvement occurred to discharge the patient. Over the next 16 weeks, the wound improved, developed a vascular base and epithelialized.

Conclusions: With a dearth of literature about stingray injuries in patients with diabetes mellitus reported, our case is unique: The patient's wound course more closely resembled a toxic inoculation than the typical puncture wound-cellulitis presentations associated with stingray injuries.

INTRODUCTION

From 1950 to 2006, the incidences of reported stingray injury in the United States ranged from 750 to 2,000 each year [1]. Most of these injuries affect the feet and/or lower extremities, typically when a victim inadvertently steps on the animal in shallow waters. A common sequela of stingray injuries is intense pain, minor soft tissue injury, and infection. Generally, puncture injuries from stingrays are resolved with hot-water immersion, local wound care, and antibiotics [2]. On rare occasions fatalities have resulted from stingray injuries that penetrate a major vessel or organ. One such case occurred with well-known naturalist Steve Irwin in 2006 when an Australian bull ray's barb penetrated his heart. Given recent reports of warmer water temperatures that enable stingrays to migrate closer to shores, the number of injuries from these animals is expected to rise [3].

Stingrays are members of the shark family. They have flat bodies that allow them to rest or hide under sand in shallow water at the beach. Stingrays are generally docile animals; they do not attack or even defend themselves, swimming away from danger when they can. However, they have tails with dorsally located spines that they use to whip over their bodies when they are disturbed. These spines are sharp and serrated, and can tear skin and soft tissues, as well as lacerate tendons and ligaments. In addition, the spines are encased in an integumentary sheath that contains proteinaceous material. When this sheath ruptures and the material is released into the wound, it causes intense pain and possible tissue necrosis [4].

We describe a presumptive stingray injury to a diabetic patient's foot with an unusual presentation and an atypical clinical course. Because of the massive slough, healing challenges, and prolonged healing, we feel this case report deserves sharing with those care providers who need to evaluate and manage injuries from marine animals.

KEYWORDS: clinical toxicology; diabetes; diving incidents; incidents; marine animals; stingray; toxins; wounds

CASE REPORT

A 36-year-old male was at an ocean beach wading in shallow, warm summer waters when he felt an intense sharp pain to his right foot. He came out of the water and noted his foot was bleeding actively from a puncture site. The patient went to an urgent care clinic, where he was given a tetanus shot, his wound was cleansed, and he was discharged home. Later that day, due to increasing pain, he presented to our hospital emergency department, where he was given insulin for a blood glucose (BG) level over 400 mg%. Of note, the patient had been diagnosed with diabetes mellitus five years prior, but had never taken medication for it nor monitored his BG levels.

His foot was soaked in warm water, which markedly improved his pain symptoms. As his foot had only a small scab with no signs of infection, he was discharged home with the medications doxycycline and metformin.

The patient returned to the hospital the next day due to increased pain, fever, and chills. He was admitted with a white blood cell count (WBC) of 26.7, tachycardia and signs of erythema, edema, and ecchymosis in the right foot consistent with infection. Piperacillin/tazobactam (Zosyn®) was administered intravenously at this time. The patient had a small linear scab about 1 cm in length embedded with small barbs consistent with a stingray spine. The patient said that he never saw what caused the wound.

While hospitalized, this wound quickly evolved to bulla formation and surrounding erythema (Figure 1). The initial culture and sensitivity report obtained from the wound showed rare growth of *Streptococcus salivarius* and *Streptococcus viridans* groups. The intravenous antibiotics were continued and the wound was covered with dry gauze.

Three days after hospital admission, a consultation for wound evaluation and management was requested. At that time the patient's WBC was 13.6 with hemoglobin A1c (HgA1c) 12.3. A bulla, partly blood and partly serous fluid, measured about 3 x 8 square cm and was located over the dorsal, lateral aspect of the right foot. Sharp debridement of the bullae and its amorphous base to the tenosynovium and periosteum of the underlying bones was completed. Silver sulfadiazine (Silvadene®) was used as the wound-dressing agent. Pain was associated with dressing changes and was managed with hydrocodone/paracetamol (Norco®).

After the debridement and eight days since the injury occurred, the patient's WBC decreased to 11.3. However, the wound base remained worrisome, with minimal development of vascular tissue (timeline, Figure 1). Negative pressure wound therapy (NPWT) was initiated on the 10th post-injury day. On Day 12, the WBC had normalized to 7.5. The wound vacuum dressing was discontinued at this time because the wound base appeared more avascular and the periwound skin had become macerated with new areas of necrosis along the proximal medial edge of the wound. Management of the wound was switched to daily moist saline dressings; then on Day 13 it was changed to acetic acid solution (AAS) moist dressings.

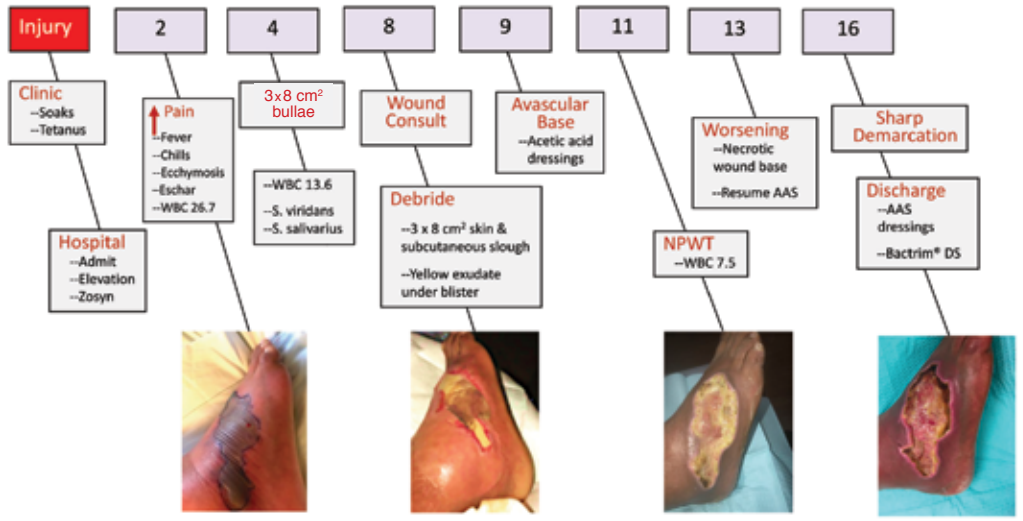
On hospital day 15 the slough areas around the periphery began to demarcate, faint signs of vascularity were appearing in the wound base, and the wound margins were starting to contract. With these improvements, the patient was discharged on the 16th hospital day on sulfamethoxazole/trimethoprim (Bactrim DS®). Daily AAS dressing changes were to continue at the patient's home. Arrangements were made for weekly follow-up appointments at our Wound Healing Center.

After hospital discharge, the wound initially stagnated (Figure 2). Management was changed from AAS dressings to the collagenase, Santyl®, and finally, again to moist saline dressings. Each wound dressing agent was used for two to three weeks. Another culture and sensitivity study obtained in the clinic showed a light growth of *Pseudomonas aeruginosa* and a heavy growth of group B Streptococcus. The patient was continued on sulfamethoxazole/trimethoprim (Bactrim DS®). After two months healthy granulation tissue began appearing in the wound base, and the wound improved at an accelerated rate (time line in Figure 2). By the time the wound base was ready for split-thickness skin grafting, enough marginal epithelialization had occurred that the decision was made to allow for coverage by secondary intention. By the 16th post-injury week, the wound site had epithelialized completely and the patient was cleared to return to work without restrictions.

DISCUSSION

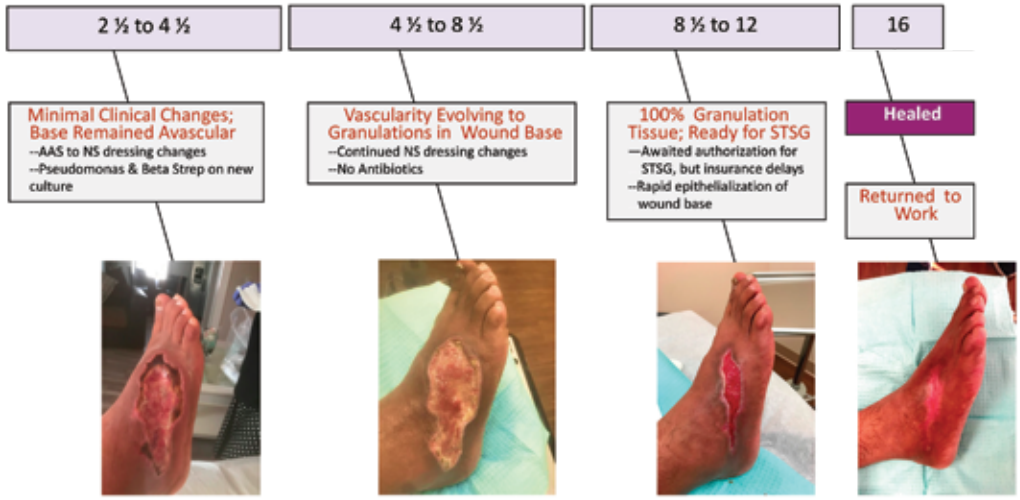
Stingray injuries can cause cutaneous necrosis of varying severities. Freshwater stingray injuries are reported to more likely cause severe skin necrosis than their saltwater counterparts [5]. Tissue necrosis has been reported in association with necrotizing fasciitis caused by *Photobacterium damselae* [6,7]. Tetanus has been reported from stingray injuries [8]. However, we were unable to find any reports of a stingray injury with extensive necrosis and prolonged healing that more closely resembled

Figure 1: Timeline of stingray injury events in hospital days



Key: **AAS** = Acetic acid solution dressing changes, **cm** = centimeters, **DS** = Double strength, **NPWT** = Negative pressure wound therapy (i.e. "wound vac"), **S.** = Streptococcus, **WBC** = White blood cell count

Figure 2: Timeline of stingray injury events in outpatient weeks



Legend: After a latency period (i.e. no improvement in the appearance of the wound base) of over a month, vascularity began to develop in the wound base. After 2 ½ months post injury, the wound was ready for skin grafting. The injury resulted in 4 months of disability

Key: **AAS** = Acetic acid solution dressing changes, **NS** = Normal Saline, **Strep** = Streptococcus, **STSG** = Split thickness skin graft

a toxic inoculation than an injury from a bacterial infection. How much the patient's poorly controlled diabetes at the time of injury contributed to the wound's course is open to question. Even though immersing the foot in hot water at our emergency department helped with pain control, as suggested by Clark, et al., it apparently did not inactivate the toxins [2]. We postulate that toxins contributed to the patient's prolonged convalescence.

In this report, the extent of tissue necrosis was surprisingly large in a wound that initially cultured only a rare growth of *Streptococcus salivarius* and *Streptococcus viridans*. Both were likely to be skin contaminants only. We hypothesize that the major skin slough and ensuing clinical course most likely conformed to a toxic reaction from the stingray injury. Eventually a satisfactory clinical outcome was achieved by focusing on making the wound

environment (i.e., selection of wound dressing agents) as physiological as possible rather than debridements to bleeding tissues, which have involved removing tendons, periosteum and decorticating the outer surfaces of the underlying bones. The delayed evaluation and management by a wound care provider (i.e., post-injury day 4) may have contributed to the patient's protracted wound healing course by allowing toxic substances to remain in contact with underlying tissues for this interval.

CONCLUSION

The consequences of diabetes mellitus probably played an important role in the prolonged healing time of the injury. The patient was initially admitted with a blood glucose level of over 400 and an HbA1c of 12.3 due to neglect of his diabetes. Two months after discharge from the hospital, with proper medication and diet management a repeat HgA1c improved to 8. This coincided with the improving clinical picture of the wound.

Any stingray puncture injury in a person with diabetes requires not only management of the injury but attention to diabetes management as well. The patient's diabetic condition most likely contributed to his wound morbidity. However, the clinical course more closely resembled a toxic reaction in tissues than infection from the stingray injury itself. Thus, the patient's diabetes status at the time of injury probably contributed to but was not the overriding consideration in the patient's prolonged wound healing course.

Conflict of interest statement
The authors have declared that no conflict of interest exists with this submission.

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LETTERS

OXYGEN TOXICITY AND DIVING HEADACHE

Dear Editor:

In their recent review [1], Burkett and Nahas-Geiger addressed the incidence of headache in diving. They related this for the most part to hypercapnia, as well as to decompression sickness, primary headache disorders, and possible diving ascent headache. They cited a study of 201 professional divers, and a definition that diving headache occurred during dives to a depth of more than 10 meters seawater [2]. The Divers Alert Network (DAN) reported a 2% incidence of headache in 374 self-reports from scuba divers [3]. Other analyses of diving headache ascribed head pain not due to personal medical conditions or accidents to CO_2 retention, cold exposure, and exertion [4-7].

We conducted two studies of central nervous system (CNS) oxygen toxicity in closed-circuit oxygen diving. In the first, we documented the symptoms reported by 473 closed-circuit oxygen divers who made a total of 2,527 training dives to a depth of 1-7 meters seawater (most of them at 3 and 5 meters) lasting between 0.5-5 hours [8]. The second investigation documented signs and symptoms from 36 diving accidents, in which divers had to terminate a dive due to severe CNS oxygen toxicity which culminated in convulsions and loss of consciousness [9].

During training for closed-circuit oxygen diving, the mean percentage of dives with headache was 4.5%. This increased linearly from 2.6% within the first hour to 8.5% in the fourth, and then dramatically to 43% in the fifth hour. However, of the 36 dives terminated due to CNS oxygen toxicity, headache was reported in 45%.

Carbon dioxide scrubber function was tested in 18 of the 36 apparatuses involved in the incidents. In 11 of the 18 there was evidence of scrubber failure, headache occurring in four of these 11 divers (36%). The incidence of headache in the dives for which there was no evidence of scrubber malfunction was 29% (2/7). All of the six divers who suffered headache had hyperventilated, but there were other divers who hyperventilated and had no headache. Of the 2,527 training dives reported in the first study, hyperventilation was reported in 2.6% (which may or may not be related to carbon dioxide accumulation). However, a higher percentage (4.5%) suffered headache. Thus, in neither of these two studies can headache be related only to CO2.

We therefore concluded that in closed-circuit oxygen diving, headache is related mainly to oxygen toxicity, suggesting that it may even be considered a mild form of this syndrome. An anecdotal example is a diver who became extra-sensitive to oxygen, suffering from headache immediately on entering the water with closed-circuit oxygen apparatus, quite the opposite of his experience when he breathed air during a dive.

Because oxygen levels in our closed-circuit system are in the region of 90% [10] (unreported measurements), the inspired oxygen tension for the majority of the training dives was 1.17 atmospheres absolute (3 meters) or 1.35 atmospheres absolute (5 meters). The incidence of headache in these dives was 3.1% and 5.5%, respectively. There were fewer dives at other depths between 1 and 7 meters seawater, however not necessarily with less headache. The inspired oxygen tension in regular self-contained underwater breathing apparatus (scuba) and in nitrox diving is close to the values in our training dives with closed-circuit apparatus. Therefore, the effect of oxygen on diving headache cannot be ignored.

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THE ISSUE: 24/7 ACCESS TO HYPERBARIC CARE

Editors note:

The publication of the paper 'Delayed hyperbaric oxygen therapy for severe arterial gas embolism following scuba diving: a case report; UHM 2019, 46(2), 197-202, by Dr. Charlotte Sadler and colleagues and the University of California at San Diego (UCSD) stated that a patient with a severe case of AGE was transferred from the University of Hawaii Hyperbaric Treatment Center (UH HTC) to UCSD due to the lack of 24/7 access to hyperbaric facilities. This prompted the following letter from UH HTC's Dr. Susan Steinemann, who contested this assertion. An answering letter from Dr. Sadler ensued as well as a discussion on the details of the transfer.

After considerable debate in this matter, speaking via email with Dr. Steinemann at UH HTC Hawaii; Drs. Charlotte Sadler and Kaighley Brett at UCSD; and Dr. Jim Chimiak, in consultation with medical specialist Daniel Nord at DAN, a discussion has emerged that highlights the issue of 24/7 access to hyperbaric care.

Despite the apparent lack of agreement in determining the exact steps in the decision tree for the treatment and recovery of this patient with severe AGE, timely care – which is essential in diving emergencies – was provided. As noted by Dr. Jim Chimiak at DAN, both facilities are to be commended for their attentiveness to their patient.

~ The Editors

THE LETTER FROM DR. STEINEMANN

Dear Dr. Camporesi and UHM readers:

I appreciated Dr. Sadler and colleagues' recount of a challenging case of arterial gas embolism ('Delayed hyperbaric oxygen therapy for severe arterial gas embolism following scuba diving: a case report; UHM 2019, 46(2), 197-202), and am grateful for the willingness of the University of California San Diego (my alma mater) to assist in these cases. However, the article inaccurately portrays the state of Hawaii as lacking a 24/7 chamber available to treat critical patients.

The University of Hawaii Hyperbaric Treatment Center (UH HTC) has been providing 24/7 emergency hyperbaric services in a multiplace chamber in Honolulu since 1982. Notwithstanding a recent unanticipated closure (10/19/17 to 1/14/18), the UH HTC has continued to provide treatment for elective and emergency cases, including critically ill and ventilated patients. The UH HTC is unique in that it is not affiliated with a hospital, which makes it substantially more difficult to provide 24/7 critical care availability for these very rare cases. Each critical patient is individually considered based upon patient condition and available resources. The hyperbaric physician who fielded the call for this patient made the (I think correct) decision to have her flown to the mainland, rather than to Oahu, based upon her multiple organ failure, the time lapse (>1 day) before hyperbaric treatment was considered appropriate, and the fact that she was a visitor from the mainland.

I endorse the sentiment iterated by Dr. Sadler and colleagues of the need to maintain emergency hyperbaric services in Hawaii. The ongoing support of the state legislature, health insurers, government entities, and the dive community are essential, as is the ability to continue collaboration with more resource-rich hyperbaric centers on the mainland.

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RESPONSE FROM DR. SADLER

Regarding the letter to UHM Editor about 24/7 chamber access in Hawaii, I spoke earlier today on the phone with Jim Chimiak and Dan Nord at DAN about this matter since DAN was consulted regarding hyperbaric chamber contacts and transport.

From the letter to the editor we all agreed that UH is taking aim at the 'lack of 24/7 access in Hawaii' statements made in several spots throughout the text.

While it is accurate that the UH chamber closed for three months – 10/19/17 to 1/14/18 – as stated in the letter from Dr. Steinemann (and verified by DAN records), the chamber had made a 'soft' reopening in January of 2018.

Rather than lack of chamber access, Dr. Steinemann notes that it was the severity of the case that prompted the personnel in Hawaii to opt to fly the injured diver to UCSD. She wrote in her letter:

'The hyperbaric physician that fielded the call for this patient made the (I think correct) decision to have her flown to the mainland, rather than to Oahu, based upon her multiple organ failure, the time lapse (>1 day) before hyperbaric treatment was considered appropriate, and the fact that she was a visitor from the mainland.'

The permanent closure of hyperbaric facilities is becoming more of an issue for timely treatment, as everyone involved in this discussion can agree. What we can emphasize here is that everyone made the best decision possible in a difficult case. Additionally, Dr. Chimiak and Dan Nord both emphasized the clear thinking on the part of the UH personnel in sending this injured diver to the facility that could provide the best care at the time: UCSD.

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HBO_2 FOR RADIATION CYSTITIS

To the Editor:

Efficacy studies are those designed to determine maximum achievable treatment response in a tightly controlled research environment, and the capacity for any demonstrated effect in everyday practice. Clinical decision-making places increasing emphasis on such high-level evidence, as do those who purchase health care. Efficacy data supporting hyperbaric medicine have long been in short supply. Practice decisions frequently rest on a mix of laboratory findings, the 'matching' of disease pathophysiology to a therapeutic mechanism, retrospective reports and uncontrolled prospective case series, alone or in any combination. When hyperbaric efficacy research does become available, then, it is deserving of particular attention, analysis and dissemination.

Oscarsson, et al. have generated one such example that serves to elevate efficacy evidence for hyperbaric oxygen (HBO_2) treatment of less severe yet common forms of radiation cystitis [1]. The term *radiation cystitis* refers to a collection of signs and symptoms (see Table). It is only the second randomized controlled trial to investigate hyperbaric oxygen HBO_2 therapy for this condition [2] and the first to demonstrate a statistically significant healing advantage over standard care. Importantly, the trial was registered with International Committee of Medical Journal Editors approved trial registries. A clinical trial (defined as prospective assignment of participants to one or more health-related interventions to evaluate outcomes) registration is essential if results are to be considered for publication in ICMJE participating journals.

Of 223 patients assessed, 87 met inclusion criteria and were subsequently enrolled. This 39% conversion ratio suggests that their reported improved outcomes are largely generalizable. Although not reported, the 'Number Needed to Treat' (NNT, an epidemiological measure used to communicate effectiveness of an intervention, and representing the average number of patients needed to be treated in order to produce one favorable outcome) was computed as an encouraging [3]. This value was the same for the subjective Expanded Prostate Index Composite (EPIC) and objective Late Radiation Morbidity Grading Scheme (LRMGS) scores, rounded up by convention from 2.56 and 2.17, respectively. An identical NNT was reported in the HBO_2 radiation proctitis randomized controlled trial [3]. One would hope that the authors' decision to exclude from 'Intention to Treat'

analysis those patients who withdrew consent immediately upon learning of their randomization would not be judged too harshly by evidence 'purists'. Shorter intervals between diagnosis and initiation of HBO_2 therapy were associated with improved responses, as were reduced radiation therapy to HBO_2 periods. This interval-related response has been reported elsewhere [4] and further supports HBO_2's earlier application. Patients suffering concurrent radiation proctitis also experienced improvement in this condition, suggesting a unique benefit of systemically delivered HBO_2 in the setting of multi-organ involvement. One would not expect a favorable response of more localized standard care to extend to other radiation-damaged organs and structures. Improved bladder findings per LRMGS scores add to the contention that HBO_2 therapy is uniquely disease-modifying [3,5,6]. This effect serves to limit the frequency of, and in many cases eliminate altogether, the remitting-relapsing consequences of more common elements of standard management directed principally at relief of symptoms such as arrest of bleeding while not overcoming its cause.

The absence of a sham component was unfortunate. Human behavior is influenced by what we know or believe, so blinding of patients to the treatment they will receive in a controlled trial is particularly important when response criteria are subjective [7], which was the case with this study. Adoption of sham controls and blinding would have further elevated this work within the evidence-based medicine hierarchy. This decision eliminated the ability to blind patients, as it did LRMGS assessors. The authors' arguments against sham were unconvincing, and neither example provided to suggest a study had been negatively impacted by inclusion of sham was correct. Sham control and double-blinding trial design was successfully incorporated into the study of HBO_2 for treatment of radiation proctitis [3]. Blinded sham controls may have also served to minimize the 16% drop-out rate post randomization in patients allocated to the control group, thereby permitting these patients to becoming eligible to receive HBO_2 therapy 'off protocol'. Attempts to evaluate de facto indications for HBO_2 at higher levels of scientific scrutiny are challenging. Providers may be ethically reluctant to commit patients to a sham exposure when clinical experience is associated with generally favorable responses. There is also the specter of medical-legal recourse. For example, a patient randomized to sham may suffer disease advancement during their study inclusion period, perhaps resulting in a fistula or bladder rupture, thereby necessitating a surgical procedure that arguably would not have been required if HBO_2 had been delivered as 'standard care'. These concerns can be lessened somewhat when treating chronic conditions by inclusion of a crossover arm. The benefit of crossover is that it assesses response in previously untreated control patients. A statistically significant improvement observed in crossover patients represents powerful confirmation of therapeutic effect. Its principal criticism is that it eliminates the potential to analyze an intervention's enduring effect. When both groups have received active treatment, long-term comparisons are no longer possible. One might argue that for treatment of late radiation tissue injury, however, any lessening or elimination of aforementioned remitting-relapsing characteristics represents an enduring effect surrogate. It is encouraging to note that eventual reporting of histologic data will have involved blinded assessors.

The full extent of radiation-induced bladder injuries was not included. The authors believed that withholding HBO_2 therapy for more advanced cases would have been unethical. This position is somewhat difficult to reconcile, as the authors note elsewhere that evidence supportive of HBO_2 as treatment for radiation cystitis 'is weak.'

References were well chosen, peer-reviewed and reflective of the current era. This is refreshing for a hyperbaric publication, where inclusion of publications that are more dated, textbook chapters and meeting abstracts is common. The former rather than the latter principally influence referring physicians and those who undertake literature reviews in order to generate clinical practice recommendations and guide reimbursement policy.

The hyperbaric dosing protocol was appropriate for this condition and slight inter-institutional variances of no consequence. Reported harms were those commonly anticipated in routine clinical practice. Each was minor in degree, largely self-limiting and supportive of the position that hyperbaric medicine is a well-tolerated, relatively safe and mastered medical technology.

Leading U.S. commercial insurers and U.S. Medicare approve the use HBO_2 therapy for radiation cystitis and reimburse accordingly. The basis for these policy decisions is the sum of modest yet consistent effectiveness data in the absence of prospective randomized efficacy studies. This new publication will certainly augment these positions. One also

hopes that reimbursement policy will evolve to recognize HBO_2 therapy as essential standard care. A recent scoping report and meta-analysis, predating the Oscarsson, et al. publication, concludes that 'using hyperbaric oxygen therapy early in the development of radiation cystitis may be associated with greater success' [8]. At present, health insurers commonly approve the use of HBO_2 therapy only after 'standard care' has proven unsuccessful. Of interest, none of the intravesical and other systemic agents used to treat radiation cystitis have been studied and proven efficacious to the level HBO_2 now enjoys.

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TABLE: RADIATION CYSTITIS MANIFESTATIONS

Dysuria
Incontinence
Frequency, urgency, decreased stream
Pain
Inflammation
Vascular telangiectasia, marked hyper-vascularity
Bullous erythema
Microscopic hemorrhage
Macroscopic hemorrhage
Clot retention, obstruction
Reduced bladder capacity
Hemorrhagic ulceration
Loss of mucosal integrity
Urethral stricture +/- fibrosis
Bladder neck contracture
Tissue necrosis
Vesicovaginal fistula; colovesical fistula
Ulceration, rupture
Death

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(407) 303-5716

* **Wound Healing Institute**
† **Florida Hospital of Tampa**
Tampa, FL
(813) 615-7160

David L. Smythe Wound Center
† **Martin Memorial Medical Center**
Stuart, FL
(772) 223-5913

Hyperbaric Medicine Department
† **Naval Aerospace Medical Institute**
Pensacola, FL
(850) 452-3409

Wound Care & Hyperbaric Medicine
† **South Miami Hospital**
Miami, FL
(786) 662-5558

GEORGIA

* **HyperbarXS at Kennestone**
Marietta, GA
(770) 422-0517

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

* **HyperbarXS at North Forsyth**
Cumming, GA
(770) 771-6400

* **HyperbarXS at St. Joseph's**
Atlanta, GA
(678) 843-5394

* **Hyperbaric Medicine Service**
† **Dwight D. Eisenhower Army Medical Center**
Ft. Gordon, GA
(706) 787-3113

Wound Center and Hyperbaric Medicine
† **Piedmont Athens Regional Health System**
Athens, GA
(706) 475-2660

Emory Wound and Hyperbaric Center
† **Emory University Hospital – Midtown**
Atlanta, GA
(404)686-2800

North Fulton Wound Care & Hyperbarics
† **WellStar North Fulton Hospital**
Roswell, GA
(770) 751-2830

IDAHO

Wound and Hyperbarics
† **St. Luke's Clinic**
Meridian, ID
(208) 489-5800

Wound Care and Hyperbaric Clinic
† **Portneuf Medical Center**
Pocatello, ID
(208) 239-2670

ILLINOIS

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

* **Wound Healing and Hyperbaric Center**
† **Edward Hospital**
Naperville, IL
(630) 527-3002

Center for Wound Healing and Hyperbaric Medicine
† **Presence St. Mary's Hospital**
Kankakee, IL
(813) 937-2273

Wound Healing & Hyperbaric Center
† **OSF Saint Francis Medical Center**
Peoria, IL
(309) 683-4300

INDIANA

Riverview Health Wound Care
Riverview Health
Noblesville, IN
(317) 776-7407

Wound Care Clinic
† **St. Vincent Evansville**
Evansville, IN
(812) 485-7659

KANSAS

* **Wound Care & Hyperbaric Medicine**
† **University of Kansas Hospital**
Kansas City, KS
(913) 588-5257

Wound Healing & Hyperbaric Center
† **Newton Medical Center**
Newton, KS 67114
(316) 804-6160

KENTUCKY

Wound Care Center-Covington
† **Saint Elizabeth Healthcare**
Covington, KY
(859) 655-1101

Wound Care Center-Ft. Thomas
† **Saint Elizabeth Healthcare**
Ft. Thomas, KY
(859) 572-3830

LOUISIANA

Hyperbaric and Wound Care Center
† **Willis Knighton Health System**
Shreveport, LA
(318) 212-5911

MARYLAND

Wound Care and Hyperbaric Medicine Center
† **Carroll Hospital Center**
Westminster, MD
(410) 871-6334

Wound Care and Hyperbaric Medicine Center
† **Northwest Hospital Center**
Randallstown, MD
(410) 496-7191

* **FMH Center for Wound Care and Hyperbaric Medicine**
† **Frederick Memorial Hospital**
Frederick, MD
(240) 566-3840

Meritus Health Wound Center
† **Meritus Medical Center**
Hagerstown, MD
(240) 313-9580

WMHS Wound and Hyperbaric Center
† **Western Maryland Health System**
Cumberland, MD
(240) 964-2626

Department of Hyperbaric Medicine
† **University of Maryland**
Baltimore, MD
(410) 328-6152

MASSACHUSETTS

Wound Healing Center
† **Anna Jaques Hospital**
Newburyport, MA
(978) 463-1303

Wound and Hyperbaric Medicine Center
† **Beverly Hospital**
Beverly, MA
(978) 921-1210

Center for Wound Care and Hyperbaric Medicine
† **Berkshire Medical Center**
Pittsfield, MA
(413) 496-6870

Center for Wound Care and Hyperbaric Medicine
† **Berkshire-Fairview Hospital**
Great Barrington, MA
(413) 854-9930

Wound Healing and Hyperbaric Center
† **Beth Israel Deaconess-Plymouth**
Plymouth, MA
(508) 732-8350

Wound Healing & Hyperbaric Center
† **Winchester Hospital**
Medford, MA
(781-396-8224

MICHIGAN

* **The Hyperbaric Medicine Program**
† **Spectrum Health**
Grand Rapids, MI
(616) 391-1269

The Center for Wound Healing and Hyperbaric Medicine
† **Beaumont Hospital-Taylor**
Taylor, MI
(313) 295-5343

Lakeland Center for Wound Care and Hyperbaric Medicine
† **Lakeland Hospital**
Niles, MI
(269) 683-8070 x8528

The Wound Healing & Hyperbaric Medicine Center
† **Detroit Receiving Hospital**
Detroit, MI
(313) 745-8453

MINNESOTA

* **Hyperbaric Medicine**
† **Hennepin County Medical Center**
Minneapolis, MN
(612) 873-4050

* **Hyperbaric & Altitude Medicine Program**
† **Mayo Clinic**
Rochester, MN
(507) 266-4602

MISSISSIPPI

Wound Care and Hyperbaric Center
Rush Foundation Hospital
Meridian, MS
(601) 703-4200

Anderson Wound Healing Center
† **Anderson Regional Medical Center**
Meridian, MS
(601) 703-5200

MISSOURI

The Wound Care Center
† **North Kansas City Hospital**
North Kansas City, MO
(816) 691-5055

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

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

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

Mercy Hyperbarics and Wound Care
† **Mercy Hospital St. Louis**
St. Louis, MO
(314) 989-1181

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

NEBRASKA

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

NEW HAMPSHIRE

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

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

The Wound Care Center
† **Portsmouth Regional Hospital**
Portsmouth, NH
(603) 433-6994

NEW JERSEY

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

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

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

Hyperbaric Services
† **Saint Peter's University Hospital**
Monroe Township, NJ
(609) 860-0008 ext 2460

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

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

NEW MEXICO

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

Sherman & Sally Dugan Center for Hyperbaric Oxygen Therapy
San Juan Regional Medical Center
Farmington, NM
(505) 609-6459

NEW YORK

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

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

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

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

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

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

* **Wound Healing Center and Hyperbaric Medicine Program**
† **Winthrop-University Hospital**
Mineola, NY
(516) 663-8498

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

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

* **Center for Wound Healing and Hyperbaric Medicine**
† **Olean General Hospital**
Olean, NY
(716) 375-7577

Wound Healing Center
† **Catskill Regional Medical Center**
Harris, NY
(845) 794-3300

Wound Healing Center
† **Orange Regional Medical Center**
Middletown, NY
(845) 333-7700

Wound Healing Center
† **Rochester General Hospital**
Rochester, NY
(585) 922-4325

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

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

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

Center for Wound Healing
† **Putnam Hospital Center**
Carmel, NY 10512
(845) 278-5683

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

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

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

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

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

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

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

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

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

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

Comprehensive Wound Healing
† **North Shore University Hospital**
New Hyde Park, NY
(516) 233-3780

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

Center for Wound Healing
† **Bassett Hospital**
Milford, NY
(607)547-6900

Center for Advanced Wound Care & Hyperbaric Medicine
† **St. Joseph's Medical Center**
Yonkers, NY 10701
(914) 378-7900

NORTH CAROLINA

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

Novant Health Wound Care and Hyperbaric Medicine
† **Forsyth Medical Center**
Winston-Salem, NC
(336) 718-6777

OHIO

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

* **Hyperbaric Medicine Program**
† **Ohio Health MedCentral Mansfield Hospital**
Mansfield, OH
(419) 526-4268

OKLAHOMA

Midwest Wound Care
† **Midwest Regional Medical Center**
Midwest City, OK
(405) 610-8056

OREGON

Bend Memorial Clinic
Bend, OR
(541) 317-4378

Hyperbaric Medicine and Advanced Wound Care
† **Providence Portland Medical Center**
Portland, OR
(503) 215-6061

Wound Healing and Hyperbaric Medicine
† **Adventist Health**
Portland, OR
(503) 252-4325

Samaritan Wound Care and Hyperbaric Oxygen Therapy Services
Samaritan Albany General Hospital
North Albany, OR
(541) 812-3660

Hyperbaric Medicine Center
† **Legacy Emanuel Medical Center**
Portland, OR 97227
(503) 413-1300

PENNSYLVANIA

Wound Healing and Hyperbaric Medicine Center
† **Reading Hospital**
Wyomissing, PA
(610) 568-3931

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

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

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

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

Wound Healing Center and Hyperbaric Medicine
† **Paoli Hospital**
Paoli, PA
(484) 565-1212

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

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

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

Guthrie Center for Wound Care and Hyperbaric Medicine
† **Robert Packer Hospital**
Sayre, PA
(570) 887-6724

RHODE ISLAND

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

SOUTH CAROLINA

* **The Department of Hyperbaric Medicine**
† **Roper Hospital**
Charleston, SC
(843) 324-3395

* **Wound Healing Center**
† **Spartanburg Regional Healthcare System**
Spartanburg, SC
(864) 560-6000

Advanced Wound Care Center
† **Summerville Medical Center**
Summerville, SC
(843) 832-5379

Advanced Wound Care Center
† **Trident Medical Center**
Charleston, SC
(843) 847-4379 ext 4462

TENNESSEE

Erlanger Wound Care and Hyperbaric Oxygen
† **Erlanger Hospital**
Chattanooga, TN
(423) 778-4027

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

TEXAS

Nix Hyperbaric and Wound Care Center
Nix Hospital
San Antonio, TX
(210) 223-1145

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

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

Wound Care and Hyperbaric Medicine Center
† **Methodist Dallas Medical Center**
Dallas, TX
(214) 447-5000

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

Southwest Center for Wound Care
Southwest General Hospital
San Antonio, TX
(210) 690-2424

Wound Care Center
† **Christus Trinity Mother Frances Health System**
Tyler, TX
(903) 531-5788

Northwest Wound Care Center and Hyperbaric Oxygen Therapy
† **Northwest Hospital**
Amarillo, TX
(806) 351-4155

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

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

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

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

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

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

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

Comprehensive Wound Center
† **Baylor Scott & White Medical Center at Carrollton**
Carrollton, TX
(972) 394-2336

UTAH

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

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

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

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

* **Wound Care and Hyperbaric Center**
† **Cache Valley Specialty Hospital**
North Logan, UT
(435) 713-1355

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

McKay-Dee Wound and Hyperbaric Center
† **McKay-Dee Hospital**
Ogden, UT
(801) 387-4870

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

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

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

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

VIRGINIA

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

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

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

Center for Wound Care and Hyperbaric Medicine
† **Centra Health**
Lynchburg, VA
(434) 200-1800

WASHINGTON

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

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

WEST VIRGINIA

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

WISCONSIN

* **Center for Comprehensive Wound Care & Hyperbaric Medicine**
† **Aurora St. Luke's Medical Center**
Milwaukee, WI
(414) 649-6577

* **Center for Comprehensive Wound Care & Hyperbaric Medicine**
† **Aurora West Allis Medical Center**
West Allis, WI
(414) 649-6609

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

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

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

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

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

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

✦

International Facilities

SINGAPORE

Naval Undersea Medical Center
Republic of Singapore Navy
Singapore
(65) 6796-4197

THAILAND

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

✦

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Sechrist Industries, Inc.
Anaheim, California
www.sechristusa.com

Baro-Serv, LLC
Tucson, Arizona
www.baroserv.com

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

The Diver Clinic
Wilmington, Delaware
https://christianacare.org

PLATINUM LEVEL

Best Publishing
North Palm Beach, Florida
www.bestpub.com

The Center for Wound Healing & Hyperbaric Medicine
Avon, Colorado
www.centerforwoundhealing.net

CutisCare, LLC
Boca Raton, Florida
www.cutiscareusa.com

Fink Engineering Pty Ltd
Warana, Queensland, AUSTRALIA
www.fink.com.au

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

GOLD LEVEL

Aurora Health Care
Milwaukee, Wisconsin
www.aurorahealthcare.org

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

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

Mayo Clinic Health System-Eau Claire Wound and Hyperbaric Medicine
Eau Claire, Wisconsin
https://mayoclinichealthsystem.org/locations/eau-claire

SILVER LEVEL

A.T.i.P Centro Di Medicina Iperbarica
Padova, Italy
www.atipcentroiperbaricopadova.it/

Centro Medico Hiperbárico de Estepona
Estepona, Málaga SPAIN
centrohiperbarico.com

Costamed
Cozumel Quintana Roo
hiperbarica@costamed.com.mx

Environmental Tectonics Corp. Hyperbaric Division
Southhampton, Pennsylvania
www.etcBioMedical.com

Evangelical Community Hospital, Wound and Hyperbaric Medicine
Lewisburg, Pennsylvania
www.evanhospital.com

Healogics Inc.
Jacksonville, Florida
www.healogics.com

HyOx Medical Treatment Center
Marietta, Georgia
www.hyox.com/

Hyperbaric Medical Services
Republic of Singapore
www.hyperbaric-singapore.com

HyperbaRXs
Marietta, Georgia
www.hbomdga.com/

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

Integrative Hyperbaric & Wound Care LLC
Vienna, Virginia
www.integrativehyperbaric.com

KingsBridge Healthcare Finance
Lake Forest, Illinois
http://kingsbridgehealthcare.com/

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

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

Mayo Clinic Health Systems Albert Lea/Austin
Albert Lea, MN
http://albert-lea/services-and-treatments/hyperbaric-medicine

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

Precision Health Care Inc.
Boca Raton, Florida
http://precisionhealthcare.com/

Restorix Health Inc.
White Plains, New York
www.restorixhealth.com

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

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

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

BRONZE LEVEL

Diving Diseases Research Center
Plymouth Devon,United Kingdom
http://www.ddrc.org/

Perry Baromedical
West Palm beach, Florida
https://perrybaromedical.com

DAN-UHMS Spring 2020 Diving & Hyperbaric Medicine Course

May 9-16, 2020

Little Cayman Beach Resort, Little Cayman, Cayman Islands

Contact: DAN CME • **Phone:** 800-446-2671 ext 1556

Fax: 919-493-3456 • **Email:** dan.uhms.cme@dan.org

Registration form at: https://www.diversalertnetwork.org/files/Reg_Spring2020.pdf

Jointly sponsored by Divers Alert Network and Undersea and Hyperbaric Medical Society, the course offers lectures, case presentations, printed support materials, and both formal and informal discussion sessions with the faculty. Tt is anticipated that attendees completing this course will be able to discuss and clinically apply facts relevant to scheduled topics. Upon completion, course participants should also benefit from a broader understanding of current issues and increased familiarity with recent, relevant scientific literature in diving and hyperbaric medicine. Learning will be reinforced by case reports from the DAN Medical Services Call Center (MSCC) Quality Assurance archives, examples from recent and ongoing diving research, and from the personal experience of the faculty.

FACULTY

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Denver Office of the Medical Examiner, Denver, CO

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Undersea & Hyperbaric Medical Society

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Thank you for your interest in joining the Undersea and Hyperbaric Medical Society. Our membership is committed to research, sound treatment and education in the fields of diving medicine, hyperbaric oxygen therapy and wound care. All members will receive a PDF copy of the *Undersea and Hyperbaric Medicine* Journal (print copies can be purchased for an additional fee); the member newsletter *Pressure*; and discounts on all UHMS meetings, publications and library services. So that we can best serve you, please complete the information below as completely as possible. Thank you for becoming a part of our membership community!

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RENEE DUNCAN Managing Editor	25 September 2019

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UNDERSEA AND HYPERBARIC MEDICINE

The Journal of the Undersea & Hyperbaric Medical Society Inc.

PRESSURE CONVERSION TABLE

Atmospheres absolute is a modified unit of pressure due to the appendage "absolute." Regarding *atmospheres absolute* we recognize the increasing simplicity to adopt ATA as the preferred unit of pressure in all our manuscripts. In addition, we encourage the use of ATM for units of partial pressure of gas or of "gauge pressure."

The units of pressure preferred for manuscripts submitted to *Undersea & Hyperbaric Medicine* traditionally have been the pascal (Pa = Newton / m^2), kilopascal (kPa), or megapascal (MPa), defined by the International System of Units (SI). We will continue to accept the SI unit pascal, kilopascal or megapascal units.

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

1 atm	=	1.013250 bar	1 atm	=	33.08 fsw	1 atm	=	10.13 msw
1 atm	=	101.3250 kPa	1 bar	=	32.646 fsw[a,b]	1 bar	=	10.00 msw
1 atm	=	14.6959 psi	1 fsw	=	3.063 kPa	1 msw	=	10.00 kPa
1 atm	=	760.00 torr[d]	1 fsw	=	22.98 torr	1 msw	=	1.450 psi
1 bar	=	100.000 kPa	1 psi	=	2.251 fsw	1 msw	=	75.01 torr
1 bar	=	100,000 Pa[d]						
1 bar	=	14.50377 psi						
1 bar	=	750.064 torr						
1 MPa	=	10.000 bar						
1 psi	=	6,894.76 Pa[d]						
1 psi	=	51.7151 torr						
1 torr	=	133.322 Pa[d]						

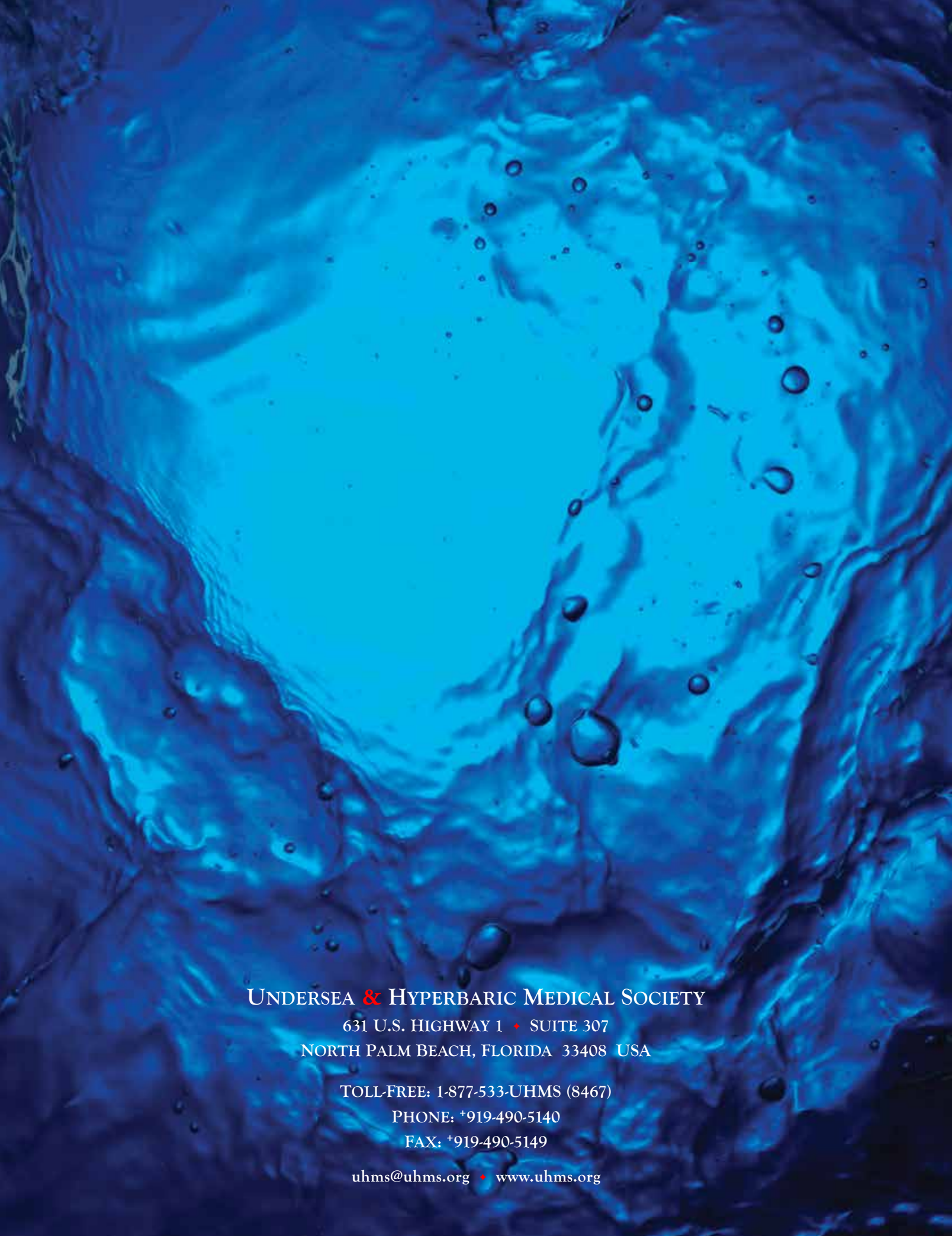
[a] Primary definition for fsw; assumes a density for seawater of 1.02480 at 4°C (the value often used for depth gauge calibration).

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

[c] Primary definition for msw; assumes a density for sea water of 1.01972 at 4°C.

[d] Signifies a primary definition [1] from which the other equalines were derived.

1. Standard Practice for Use of the International System of Units (SI). Doc. E380-89a. Phila., PA: Am. Soc. for Testing and Materials, 1989.



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