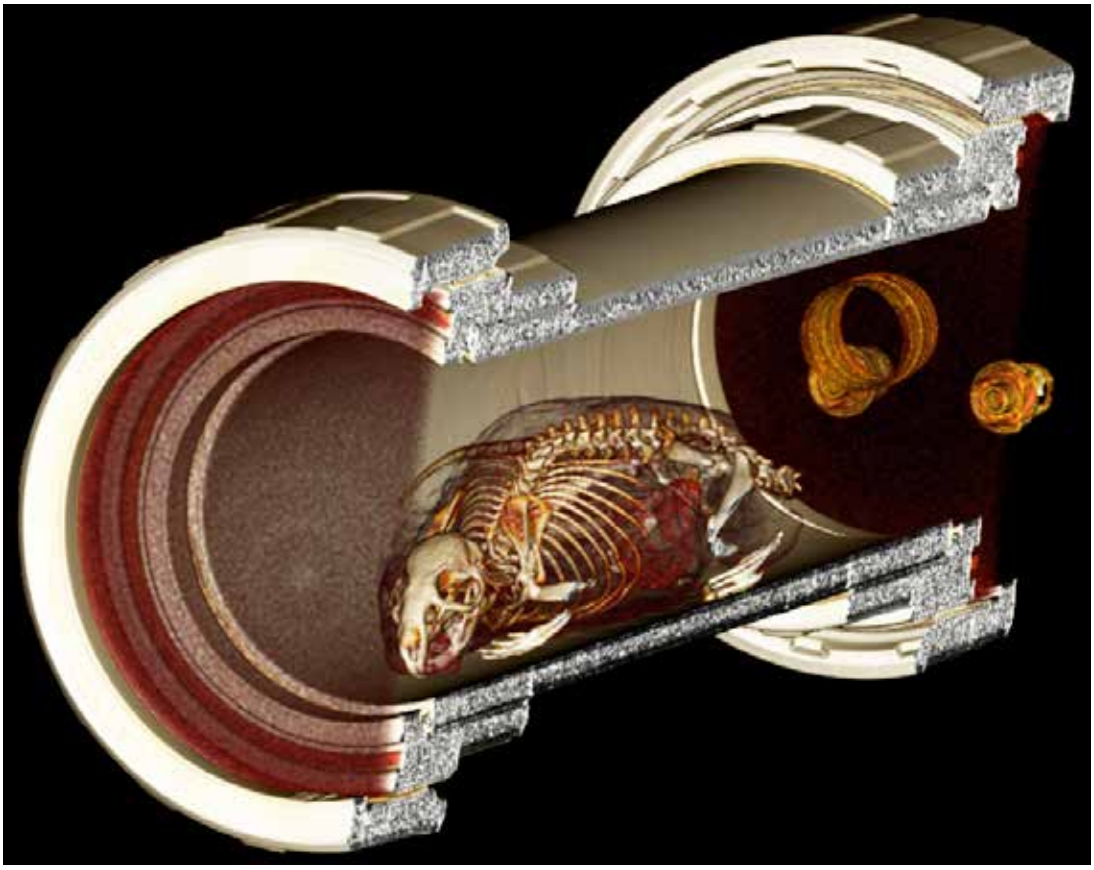
Diving and Hyperbaric Medicine

The Journal of the South Pacific Underwater Medicine Society and the European Underwater and Baromedical Society

SPUMS

Volume 45 No. 4 December 2015

EUBS



Imaging small animals under pressure

Treatment patterns for osteoradionecrosis of the jaws

The vascular endothelium, aging and diving

Calculating gas consumption during diving

More data needed on cost-benefit of HBOT

CSF markers of CNS injury in mild DCS

Print Post Approved PP 100007612

ISSN 1833-3516, ABN 29 299 823 713

PURPOSES OF THE SOCIETIES

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

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Diving and Hyperbaric Medicine **is published jointly by the South Pacific Underwater Medicine Society and the European Underwater and Baromedical Society (ISSN 1833-3516, ABN 29 299 823 713)**

The Editor's offering

All our readers will have a basic understanding of the Ideal Gas Law and of diabatic and adiabatic phenomena, either from their school-days physics or from their diving/diving medicine training.[1,2] Those working in hyperbaric chambers experience thermodynamic affects every day with changes in temperature – warming with compression and cooling with decompression – and pressure – the fall in pressure after compression if the operator does not 'top up'), as the heat generated from compression dissipates into the heat sink of the chamber's metal walls. Adiatatic and diabatic phenomena will also occur during diving and their implications for accurate calculation of instantaneous gas consumption are discussed in detail in the paper by Schellart et al.[3]

Another mathematically challenging paper for some will be the technical report on validating a new concept in small animal research, that of a pressure chamber system that allows modern-day imaging during pressurisation up to 1.013 MPa.[4] This has the potential to provide exciting new insights into our understanding of physiological phenomena under pressure about which, till now, we have only been able to surmise from pre- and post-dive study.

The returns of answers to the Continuing Professional Development units have been disappointingly very low. As a result, the Editorial Board at its meeting in Amsterdam in August made the decision to discontinue these. The unit in this issue, on women in diving will be the last. I would like to thank the many contributors who have volunteered to provide educational material for these over the past six years.

Whilst on a note of appreciation, it is also an appropriate time for me to acknowledge all our Editorial Board stalwarts, some new to the Board in the past year or so, and those who have served *Diving and Hyperbaric Medicine* (DHM) for many years, way back into the time before 2007 when it was called the *SPUMS Journal*. Likewise, over 100 scientists and physicians have given of their time freely to review submissions. Whilst many may have only refereed one or few papers over the years, others contribute regularly. Such collegiate support is absolutely essential to the quality and survival of DHM, and an editor is totally reliant on this willingness to contribute time, effort and expertise. We do not have the time or space to list everyone who contributes in any given year, but rest assured that your work is very much appreciated, not only by us, but also by authors. Almost every submission requires some degree of revision before publication and there is not a single paper that I have dealt with over my 13 years as Editor that has not benefitted from peer review.

During these 13 years, DHM has grown in quality and international reputation. It is now indexed on both MedLine/PubMed and SciSearch®, giving it an Impact Factor (IF) very similar to that of the UHMS's publication, *Undersea and Hyperbaric Medicine*. None of this could have happened without our authors submitting their work for consideration. Without them there is, of course, no journal. Not unnaturally there is often pressure to publish in major mainstream journals, but it is important that EUBS and SPUMS members support their own specialty journal as much as they possibly can. Only by doing so will DHM continue to grow in stature and Impact Factor. Whatever one thinks about IF, it is often the yardstick by which researchers' publications are measured by their employing institutions. A concerted effort to support DHM is still needed from you all.

Today, just before writing this *offering*, I signed a new contract as your Editor for 2016 through 2018. I thank the societies for this further opportunity to serve your Journal, which I will continue to do to the very best of my ability (health and mental faculties willing!). Despite the warning that "*nearly every white-collar job that involves sitting in front of a computer manipulating information*"[5] is under threat and that computers can now turn facts into perfectly serviceable journalism, I believe there will be a role in medical journalism for the likes of myself for some time! Unfortunately this period starts in a climate of disagreement over the unilateral decision by EUBS, without consulting their co-publishers SPUMS or others such as myself, to change the production and distribution of DHM by providing only the web-based pdf to some of its members. However, in 2016, DHM will continue to be distributed by this office to all members of both societies in print, not electronic form. The SPUMS Executive has proposed to EUBS that DHM moves to a proper, full e-journal at the start of 2018.

I wish you all the very best of health, safety and professional success for 2016. Don't take the paper by 'Prancer' Blogg et al. too seriously, as happened with a previous spoof article.

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Michael Davis

Front page image (courtesy Hansen K et al. is of a CT image of a rat positioned inside a CT-, PET- and MRI-compatible, rodent-sized pressure chamber (pressure range to 1,013 kPa) developed for baromedical research.

Commentary: Hyperbaric oxygen treatment for wounds – evidence and the Sword of Damocles

Increased access to any treatment sensibly follows the clinical and cost benefit being established. For many treatments this requires multiple, high-quality clinical trials and supporting cost analysis. Cost analysis may be applied to a single treatment or used to compare two or more treatments. Clinical efficacy and cost benefit are best scrutinised and validated by publication in the peer-reviewed literature. True peer review is most effectively achieved 'after publication' by the wider scientific community, i.e., the journal readers. However, initially an editor, usually advised by referees, is asked to make a judgment on a paper's suitability for publication. It follows that medical journals are in a position of power and responsibility. Researchers and editors know publications are currency; effectively they are the equivalent of academic bitcoins.

Regarding the paper in this issue by Santema et al.,[1] the same authors, in designing a prospective randomised controlled trial (RCT) of the role of hyperbaric oxygen treatment (HBOT) in diabetic wounds, included the name "*Damocles*" in that trial's title.[2] Readers will perhaps appreciate from my comments below as a referee for the Santema et al. paper, that behind the scenes "*the Sword of Damocles*" (an allusion to the imminent and ever-present peril faced by those in positions of power) hangs over researchers, treating physician, journal editors and referees alike.

Whilst positive about its content, upon reflection, my concern was the anticipated reception of this paper by the journal readership. This is, of course, a matter for the Editor; however, herewith is my reasoning. Further to the body of published work by Bennett et al.,[3] and others that has focused attention on the lack of good quality evidence for the use of HBOT for most indications, I think this regrettable state of affairs is now both known and accepted by mainstream healthcare purchasers and providers.[4–7] I speculate that all these bodies already acknowledge and accept this manuscript's conclusions. Accordingly, this situation detracts from an opportunity for it to stand out from existing publications. The authors are addressing this known lack of evidence with their planned DAMOCLES multicentre RCT.[2] Others in mainstream medicine in a position to design and implement clinical research (to whom the paper is presumably aimed) will also be acutely aware of the shortcomings in the available evidence.

Accepting the sample size required for economic evaluation may be greater than that required to establish only clinical effectiveness, it remains the case it would be all but impossible to secure research funding for a trial in the absence of such analysis. This means the conclusions of the present paper are already widely acknowledged. If one accepts the above, it follows that its impact on the journal readership will be relatively light.

The journal`s review process asks referees to consider if the manuscript is "*within the journal's scope*", and about "*the importance (clinical or otherwise) of the work*". I think this paper is within the scope and is important. However, in the light of the known and accepted need for further research that includes an economic evaluation, I find myself questioning the 'importance' and 'utility' to the journal readership of the information provided.

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Key words
Wounds; hypebaric oxygen therapy; cost-effectiveness; editorials

The Presidents' pages

Jacek Kot, President, EUBS

I am the fifteenth person to have the honour of reporting for duty as your President in the 45-year-long history of the EUBS. It is now some time since our Annual Scientific Meeting (ASM) in Amsterdam, The Netherlands. As always, the city was beautiful, and the time there extremely busy. Rumour has it that this was due to *Sail 2015*, which coincided with our conference, but this is only part of the truth in that we had a record number of registrants to a non-conjoint EUBS meeting – around 350! Indeed, the meeting was very successful at every level – the science, the excellent organisation, the social events and even the weather. An extensive report (prepared by Jordi Desola, who is one of very few, if not the only one who has participated in every EUBS meeting, including the previous one in Amsterdam in 1990) will appear on the society website. A brief perspective of the meeting from him also appears later in this issue. From my perspective, I would just like to say to the organizers: "*Good job, Albert and Rob!*" and, of course, their whole team, so friendly and professional.

Our Society is a living organism and as so, it is evolving. As always, there is a new blood coming to our steering committees to lead actions and 'older' colleagues are moving to the back seats, just providing their wisdom and experience. At elections this year, Karin Hasmiller from Germany takes up the position of Member-at-Large 2015 and Ole Hyldegaard from Denmark assumes the position of Vice-President to become President in three years. This means that Lesley Blogg has ended her term as Member-at-Large but, fortunately for us, she stays on the Executive Committee as European Editor of *Diving and Hyperbaric Medicine*. Tino Balestra steps down to become the Senior President (formally known as Immediate Past President). In order to keep our youngest colleagues interested in the organisation of our Society, we have created a committee devoted specifically to research education; Kate Lambrechts from France will lead this process, with Tino Balestra helping to coordinate the work of this exciting new committee as its chairperson. All members having ideas on research training should share their thoughts with them.

There are also some changes to our membership plans. Firstly may I remind you that you do not need to renew your membership before the end of 2015, as the Society's fiscal year has now moved to coincide with the calendar year. For most members, this means that their last membership period will last for one and a half year instead of only one year; for sure, a clear benefit for you. In addition, during the EUBS 2015 General Assembly, it was agreed to modify the membership plans, including an increase in the membership fee. Indeed, this fee has been stable for the past eight years, so this is a necessary evolution to reflect increased costs of (amongst other things) producing a high-quality scientific journal. In the past, some members have expressed their clear wish to switch to a 'paperless' version of DHM and stop receiving the print copy, staying simply with on-line access to the pdf file. So this option has now been added to the membership plan, allowing for a slightly lower membership fee. All other full members will continue receiving the quarterly paper Journal as usual, and will, of course, also have access to the pdf file in the members-only area of the EUBS Website. This adds more flexibility to our membership plans allowing saving some of your pocket money. Moreover, in that way we will see in the next few years how many members are willing to switch to a 'real' e-Journal (not simply on-line access to the pdf file), planned for the future.

Developing on our friendly and professional cooperation with other Societies, mostly with SPUMS and SAUHMA, and following the very successful tri-continental meeting in Reunion in 2013, we have already started preparation for the next tri-continental meeting, preliminarily scheduled for 2018 – details will come later. Regardless of the joint conference of EUBS, SPUMS and SAUHMA, we wish to expand further our cooperation with other international (UHMS) and national (within and outside Europe) societies and organisations, formalizing these relationships with 'Memoranda of Understanding' and 'Letters of Intent' – always on a reciprocal basis.

I do not want to bother you too much with administrative details, so I strongly suggest you stay connected with the Society through our website, <www.EUBS.org> where all the society news and information is available for those interested.

At the end of my first President's page I would like to repeat my declaration, which I have already presented at the end of the Amsterdam Conference, when I took over the position of the President – this is my service to the Society, please let me know your concepts and ideas in order to continue ennobling EUBS. You can reach me at:
<jacek.kot@eubs.org>

Key words
Medical society; general interest

David Smart, President SPUMS

This year, I attended all three major scientific meetings in diving and hyperbaric medicine (DHM), those of SPUMS, UHMS and the EUBS. Despite differences in format, all share in common high-quality scientific content, positive international networking and a consistent optimism for the future of DHM. Congratulations to all conveners for putting together such terrific events, especially Cathy Meehan for her efforts with the SPUMS ASM at the remote venue of Palau. I met with many international colleagues, further enriching my perspective of our speciality. After Amsterdam, I attended the *Ultrasound in Diving Medicine* workshop, hosted at the Karlskrona Swedish Naval Base; this exemplified what is achievable when like-minded scientists assemble in a world-class facility. Best-practice guidelines for ultrasound research in diving medicine will be published in the near future to enable greater consistency of ultrasound practice.

Apparent in the 'global economy' is the rapid sharing of information between health agencies, and many specialists in hyperbaric medicine are experiencing similar issues with funding and fundamental questioning (even threatening) of the existence of the speciality. The key to dealing with these threats is high-quality clinical hyperbaric research using randomised controlled trials. In addition, we need to demonstrate the cost-effectiveness of hyperbaric oxygen treatment (HBOT) as a therapeutic intervention. Demonstrating clinical benefit is not enough to satisfy the circling health economists. More multicentre international clinical trials are needed if the speciality is to survive the scrutiny of 21st century health provision.

It is disappointing that the same high standards of data quality and research methodology have not applied when health bureaucrats analyse HBOT. A recent article by Duckett et al. warrants further comment.[1] Entitled "*Identifying and acting on potentially inappropriate care*", this article summarises a more detailed Grattan Institute report, and its methodological supplement.[2,3] A number of procedures were declared "*do-not-do*", including HBOT. The translation process to a paper in the *Medical Journal of Australia* concealed huge flaws in the data and methods which produced completely inaccurate and misleading conclusions about HBOT. The authors claimed "*more than 4,500 people get hyperbaric oxygen therapy when they do not need it*", and made alarmist claims without supporting data: "*these numbers alone do not describe the full extent of the problem*".[1] Unfortunately the paper was not peer-reviewed by hyperbaric specialists, which would have identified the serious flaws that led to their misleading conclusions:

- Numbers for patients receiving HBOT were completely inaccurate. The Hyperbaric Technicians and Nurses Association Conference in 2011 recorded 1,276 patients received HBOT in total in Australia during the time period of Duckett's data collection – less than one third of the alleged inappropriate patient numbers.
- Data for procedures and diagnoses were derived from hospital admission statistics. The methodology assumed each admission was a different patient, rather than being part of a course of treatment, demonstrating a complete lack of understanding of HBOT clinical practice.
- Major inaccuracies were identified in the hospital procedure codes for HBOT used to populate the study. One particular code, 9619100, described delivery of HBOT ≤ 90 minutes; a treatment schedule that is not used in Australia. This further showed disconnection with actual clinical practice.
- Reviews of coding from single centres have demonstrated inaccuracies in up to 25% of admissions, including missing the actual reason why HBOT was provided.
- Coding did not accurately record the reason for HBOT when it was delivered for prophylaxis of osteoradionecrosis, hence it may appear that HBOT was used to treat cancer.
- Soft-tissue radiation necrosis and non-diabetic problem wounds were funded by Medicare and completely legitimate at the time of data collection but were misrepresented by Duckett. These were likely to make up the majority of alleged "*inappropriate*" cases identified by the study. Given the experience of the authors, this basic error is extraordinary.
- No raw data were provided for the frequencies of specific medical conditions receiving HBOT, effectively concealing the data and prevented forensic scrutiny. It falsely implied that HBOT was provided to large numbers of patients outside the Medicare-funded list.

Further detailed critique is in the pipeline. It is of serious concern that poorly constructed science analysing flawed HBOT metadata reached publication without hyperbaric specialist review. Based on their conclusions, the authors even recommended punitive action against clinicians! It is essential that evidence presented by bureaucrats meets the same standards that they demand of clinicians. It must be accurate, with transparent source data and sound methodology. The Grattan Report fails in all respects.

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Key words

Medical society; hyperbaric medicine; cost effectiveness; general interest

Original articles

Correction for adiabatic effects in the calculated instantaneous gas consumption of scuba dives

Nico AM Schellart and Jean-Claude Le Péchon

Abstract

(Schellart NAM, Le Péchon J-C. Correction for adiabatic effects in the calculated instantaneous gas consumption of scuba dives. *Diving and Hyperbaric Medicine*. 2015 December;45(4):221-227.)

Introduction: In scuba-diving practice, instantaneous gas consumption is generally calculated from the fall in cylinder pressure without considering the effects of water temperature (heat transfer) and adiabatic processes. We aimed to develop a simple but precise method for calculating the instantaneous gas consumption during a dive.

Methods: With gas thermodynamics and water/gas heat transfer, the instantaneous released gas mass was modelled. In addition, five subjects made an open-water, air, open-circuit scuba dive to 32 metres' sea water. Depth, cylinder pressure and water temperature were recorded with a dive computer and gas consumption was calculated and compared using different methods.

Results: After descent in open-water dives, the calculated gas mass in the cylinder was the same as calculated from cylinder data, suggesting that the model is adequate. Modelled dives showed that adiabatic effects can result in considerable overestimate of the gas consumption, depending on the dive profile, exercise-dependent pulmonary ventilation and the cylinder volume. On descending, gas thermodynamics are predominantly adiabatic, and the adiabatic correction of ventilation is substantial. During the dive, the adiabatic process (at the start 100%) decreases steadily until the end of the dive. Adiabatic phenomena are substantially different between square and saw-tooth profiles. In the emergency situation of a nearly empty cylinder after a square-wave dive involving heavy physical exertion, the adiabatic effect on the cylinder pressure is generally > 20%. Then, with a strongly reduced consumption at the start of the ascent, heat inflow produces an increase of cylinder pressure and so more gas becomes available for an emergency ascent.

Conclusion: Adiabatic effects, being indirectly dependent on exercise, the profile and other conditions, can be substantial. The developed method seems sufficiently accurate for research and possibly for reconstruction of fatalities and is implementable in dive computers.

Key words

Gases; gas supply; universal gas law; thermodynamics; models; ascent; computers – diving

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Introduction

In scuba-diving practice, instantaneous and total dive gas consumption is generally calculated from retrieved cylinder pressures, implicitly assuming isothermal gas thermodynamics in the cylinder. This classical method is correct for the post-dive calculation when at the time of cylinder pressure readings, the temperature of the gas in the cylinder is the same pre- and post-dive. Calculation of instantaneous gas consumption is more complicated. This requires data on the actual temperature in the cylinder; however, this cannot be calculated from the universal gas law ($PV = nRT$) applied to the cylinder gas (V – volume, P – pressure, n – gas mass, R – universal gas constant, T – absolute temperature).

Thermodynamically, there are two extreme conditions: the purely isothermal and the purely adiabatic one. When the cylinder is considered as a system with an infinitely fast heat transfer between cylinder gas and ambient water (T is water temperature) the process of gas release is isothermal; the universal gas law holds and n can be calculated. However, when the cylinder is considered as thermally isolated, the gas temperature T decreases: the process is adiabatic. Now, n and T are unknown. In practice, the problem is more complicated since such pure conditions do not exist. Any pressure drop involves a mixed isothermal/adiabatic process.

Various types of dive computer (DCS) provide some measure of the level of consumption during the dive, but ignore adiabatic pressure and temperature effects. With constant depth, pulmonary ventilation and ambient temperature, the gas in the cylinder always cools down due to adiabatic expansion. Cold stress and work load increase ventilation and, thereby, increase the adiabatic effect. This particularly applies in situations with, for example, strong currents, heavy exercise or emergency stress. The longer the gas release (with some flow) lasts, the greater the drop in temperature; this also applies for depth since gas flow increases with depth. When not considering the effect of cooling due to adiabatic expansion, the calculated consumption can be substantially overestimated.

Points that need to be considered for correct reconstruction of the instantaneous consumption are:

- Cooling of the gas in the cylinder due to adiabatic expansion;
- Heat transfer from the ambient water to the gas in the cylinder that may counteract the adiabatic cooling;
- Heat transfer between gas and water due to a change in water temperature (with depth) resulting in heating or extra cooling of the gas;
- 'Quasi-consumption' when the buoyancy control device (BCD) is inflated.

Since, in the present theoretical design and in actual dives, the gas mass that leaves the cylinder is of interest, corrections to obtain the physiological consumption (especially the quasi-consumption for pressure equalizing the lungs) are omitted. During the actual dives, 'quasi-consumption' can be avoided by preventing the BCD from being inflated with cylinder gas. Taking the first three points into account, it can be shown that the released gas mass can be calculated with a simple computation from three quantities: cylinder pressure, water temperature and depth, provided that the half-time (assuming an exponential mechanism) of the heat transport process is known. We also will show that the three quantities can be obtained with non-expensive but sufficiently accurate equipment. From the release, the instantaneous ventilation, expressed in ambient L·min^{-1} (aL·min^{-1}) at 37^{O}C (the alveolar temperature), can be calculated with the necessary corrections during the descent: BCD-correction, equilibration of the lung, airways, sinuses, mouthpiece and mask.

To evaluate the method of calculation and its usefulness it is applied to both theoretical dives and actual open-sea dives. Attention will be paid to the following model parameters: profile, ambient gas flow (mimicking level of exertion), cylinder volume and water temperature. In summary, the aim of this study, new in diving-related computation and relevant for diving physiology, is to develop a simple, cheap but accurate method to calculate gas consumption at any moment during a dive.

Methods

MODELLING

From the universal gas law $PV = nRT$ and the expression of thermodynamics, $PV^{\gamma} = constant$ where γ is the thermodynamic C_P/C_V ratio, it can be calculated that:

$$P_{a,j} = n_j^{\gamma}.(R/V)^{\gamma}.T_{j-1}^{\gamma}.P_{t,j-1}^{(1-\gamma)} \quad [1]$$

where C_P and C_V are the specific heat at constant pressure and constant volume respectively ($C_P = C_V+R$), $P_{a,j}$ the j-th cylinder pressure after j-th inspiration (j = 1, 2 …) and adiabatic cooling due to decrease of the cylinder pressure, n_j – gas mass, T_j – measured water temperature and $P_{t,j}$ – measured cylinder pressure. With an exponential approximation of heat transfer to the cylinder gas, it can be calculated that for the j-th time interval Δt it holds that:

$$2^{-\Delta t/h}.P_{t,j-1}(n_j/n_{j-1})^{\gamma} + n_j.(1-2^{-\Delta t/h})RT_jV^{-1} - P_{t,j} = 0 \quad [2]$$

where h is the half time of heat transfer between ambient water and gas in the cylinder (assumed homogeneous temperature). Since Eq. [2] has no analytic solution in n_j, n_j must be solved numerically. From n_j, the instantaneous gas volume flow is known and hence the consumption.

Before presenting the results of actual and simulated dives, the contribution of the adiabatic effect in the mixed process, hence with heat transport, is calculated for model simulations with a constant depth, a constant flow (in ambient units), and a constant water temperature (T) of 300 K (27^{O}C). These outcomes are compared with the isothermal condition used in dive computers (DCs). With a given constant consumption, being Δn mol/Δt, after rewriting Eq. [2], the cylinder pressure can be found with:

$$P_{t,j} = P_{t,j-1}.2^{-\Delta t/h}((n_0 - j\Delta n)/(n_0 - (j-1)\Delta n))^{1.4} + (1 - 2^{-\Delta t/h})RT(n_0 - j\Delta n)V^{-1} \quad [3]$$

with n_0 the gas mass at the start of the dive and h = 80 s (when V = 0.012 m^3). h was estimated from pool experiments (≈ 20^{O}C cylinder/water temperature difference) and was close to a physical model estimate (personal communication, van Grol HJ, 2014). h is slightly dependent on cylinder dimensions and material and on current (swimming against a current). With h = 0, i.e., infinitely fast heat transfer, the process is pure isothermal and, with h = ∞, i.e., no heat transfer, the process is pure adiabatic.

The mixed process can be quantified by three variables, the absolute adiabatic pressure effect, (*AP_effect*, bar), the relative adiabatic effect (*A_effect*, %) and the adiabatic fraction (*A_fraction, %*):

$$AP\_effect = P_{iso} - P_{mixed} \quad [4a]$$

(subscript iso means isothermal)

From a practical point of view, the evolution of *AP_effect* is the most relevant adiabatic phenomenon since it is a measure of the 'extra' pressure that becomes available when the gas is warmed to the ambient temperature:

$$A\_effect = 100(P_{iso} - P_{mixed})/P_{iso} = 100(T_{iso} - T_{mixed})/T_{iso} \quad [4b]$$

This equality directly follows by applying the universal gas law. *A_effect* gives the relative decrease of pressure and temperature relative to the isothermal pressure and temperature:

$$A\_fraction = 100(P_{iso} - P_{mixed})/(P_{iso} - P_{adia}) \quad [4c]$$

(subscript adia means adiabatic)

By applying the gas law, the consumption per minute (Eq. [2] and [3] use Δt, here 4 s) of the actual dives was calculated with $\tilde{V}$ = 387 ($n_{j-1} - n_j$)/(0.1 depth +1) aL·min^{-1} (body temperature, depth in msw). Since air and nitrox have the same C_P/C_V

ratio (γ = 1.4) and the same thermal conductivity, all results also apply to nitrox. This does not hold for helium mixtures since decompression of helium gives adiabatic heating above 51 K (the Joules-Thomson effect), not cooling. Consequently, the adiabatic effects of helium and nitrogen (or oxygen) counteract each other. Therefore, adiabatic phenomena in cylinders containing heliox or trimix do not need to be considered.

OPEN-WATER DIVES

Five, fit subjects volunteered to make a single, recreational, no-decompression, air scuba dive. Ethical approval was not required by the Medical Ethical Committee of the University of Amsterdam (Project W15_204, Decision #15.0262). However, all subjects provided informed consent. The intended profile characteristics and the conditions were: descent rate 20 m·min^{-1}, maximal diving depth (MDD) 30 meters' sea water (msw) for 2 min, with a gradual saw-tooth ascent over 40 min; 12-L aluminium cylinders, wetsuits and the same UWATEC *Galileo Luna* DC. Depth (resolution 0.01 msw; error at most -0.3 msw), cylinder pressure P_t (resolution 0.25 bar), and water temperature T_j (resolution 0.4^{o}C, error at most -0.4^{o}C) were retrieved from the Galileo with sample intervals (Δt) of 4 s. The subjects were accompanied by an experienced buddy.

Before starting the descent, the cylinders were temperature equilibrated with the ambient water temperature for 8 min. At MDD, the BCD, not used until then, was orally inflated by the buddy. After leaving MDD, the subject buddy-breathed for about 7 min to equilibrate the temperature of his/her cylinder (eliminating the effect of adiabatic cooling), in order to validate the model calculation of the consumption at the instant of leaving MDD. During the remainder of the dive, subjects breathed from their own cylinder.

In the open sea, temperate (summer) and tropical water temperature generally decreases with depth. The half time of the Galileo temperature sensor appeared too large (ca. 40 s with a swimming speed of 1200 m.h^{-1}) to obtain precise recordings of the changing water temperature during the descent in order to validate the method. Since the ascent was so slow (1–2 msw·min^{-1}), the temperature recorded was considered to be water temperature. These logged temperatures (as a function of depth) were also used for the depth-temperature relation during the descent.

Results

MODELLING

As a reference, a ventilation flow rate of 17 aL·min^{-1} was used (see Results, open-sea dives). With an isothermal process ($h = \infty$), a constant depth, constant gas flow and constant ambient temperature during the whole simulation, P_t diminishes linearly with time (ignoring the small effect of the breathing cycle). P_t is proportional to the level of gas flow and to ambient absolute pressure.

Figure 1

Evolution of adiabatic effect. Adiabatic effect (reverse-plotted at left axis) and pure isothermal cylinder pressures (right axis). The upper stippled straight line presents the isothermal cylinder pressure P_t (right axis) at a depth of 1 msw and a flow rate of 17 aL·min^{-1}. The lower stippled straight line is for 34 msw depth with 42.5 aL·min^{-1}. The upper and lower solid curves show the difference in cylinder pressure between the mixed and the isothermal process relative to the isothermal pressure (left axis, in %; same depths and flow rates); cylinder volume 12-L

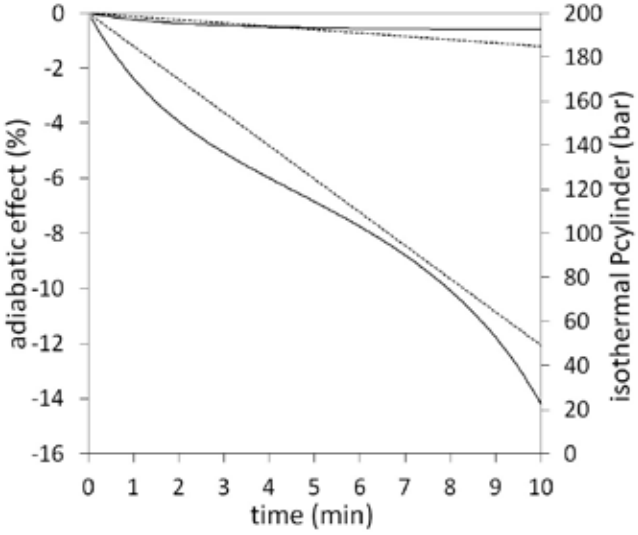
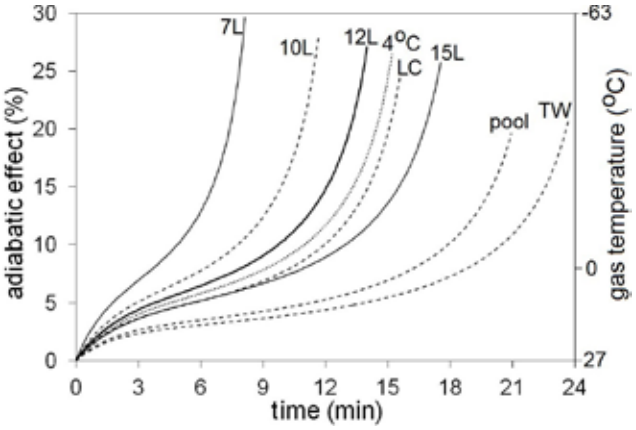


Figure 1 (P_t at right axis; stippled curves), illustrates this for 1 msw with 17 aL·min^{-1} and for 34 msw with 42.5 aL·min^{-1} (ratio of absolute pressures = 4 and ratio of ambient flows = 2.5). With any adiabatic release, the P_t always diminishes faster than with a pure isothermal process. The solid curves shown in Figure 1a (left axis) give *A_effect* for the two depths. The upper solid curve (1 msw, 17 aL·min^{-1}) indicates that for this low release the adiabatic cooling is nearly compensated for by heat inflow from the surrounding water. The lower solid curve indicates (with the 10x faster gas release) that *A_effect* cannot be ignored. Yet, between 5 and 10 min heat inflow dominates; *A_fraction* ≈ 35%. At 5 min with isothermia, the pressure left is 125 bars, whereas in the mixed case it is 8.5 bars lower. Here, *AP_effect* becomes smaller after 6 min, but *A_effect* is still increasing (from 6.5% at 5 min to 13.5% at 10 min).

Figure 2 shows the influence of cylinder volume, water temperature, depth and consumption on *A_effect* (left axis) under constant conditions (mimicking a square-wave dive with descent and infinitely fast ascent). The adiabatic cooling (right axis) is presented for a water temperature of 27^{o}C. At the moment that a cylinder pressure of 50 bar is reached, the effect is about 9% and > 20% with an 'out of air' situation (10 bar reached; the top end of the curves). Even in shallow

Figure 2

Adiabatic effect as function of time with various cylinder volumes, water temperatures and exertion levels. 7-L, 10-L, 12-L and 15-L cylinder volume with 34 aL·min^{-1} at 34 msw and 27^{o}C; 4^{o}C – the same for 12-L cylinder but 4^{o}C water temperature; LC – low consumption (26 aL·min^{-1}), 34 msw, 27^{o}C; TW – temperate water 13^{o}C, 10-L cylinder, 26 aL·min^{-1}, 20 msw; Pool – 27^{o}C, 51 aL·min^{-1}, 3.8 mfw. N.B. All dashed curves are for 10-L cylinder. Right axis gives the cylinder gas temperature for the curves with 27^{o}C water temperature



water, high gas consumptions give a similar effect as with an ordinary dive (20 msw, 25 aL·min^{-1}) in temperate water (compare 'pool' and 'TW' curves).

Figure 3 presents *A_effect* for the four combinations of 17 and 42.5 aL·min^{-1} and 1 and 34 msw. At 1 msw, irrespective of the consumption level (curve 1 and curve 3) and with 17 aL·min^{-1} at 34 msw (curve 2) *A_effect* is almost irrelevant. With 42.5 aL·min^{-1} at 1 msw, after 10 min *A_effect* is only about 3% lower than the isothermal pressure (curve 3). However, at 34 msw a 15% difference is seen (curve 4) and during 10 min *A_fraction* changed from 100 to 33%.

The simulation of curve 5 is basically the same as for curve 4, but periods of 30 s at a ventilation rate of 72 aL·min^{-1} were inserted at 2 and 6 min. The second 30-s period gives a large, long-lasting adiabatic effect that can only be counteracted by a very low gas consumption. After t = 10 min, with a consumption of 10.6 aL·min^{-1} (swimming speed nearly zero[1]), the temperature increases quickly because heat inflow overwhelms the ongoing but small adiabatic cooling effect.

The above examples respect constant-consumption simulations. The next one shows a calculated simulated dive to 34 msw with descent and ascent included for a pure adiabatic, pure isothermal and a mixed process (Figure 4). After t = 5 min, the consumption changes from 17 to 42.5 aL·min^{-1}, resulting in a larger difference between the adiabatic and isothermal pressures and a sudden large increase in *AP_effect* (thick dashed curve). During the descent, the thermodynamics of the gas is predominantly

Figure 3

Evolution of the adiabatic effect (left axis) and absolute cylinder gas temperature (right axis). Curves: #1 1 msw / 17aL·min^{-1}; #2 34 msw / 17 aL·min^{-1}; #3 1 msw / 42.5 aL·min^{-1}; #4 34 msw / 42.5 aL·min^{-1}; #5 as #4 but two 30 s periods of 72 aL·min^{-1} and after t = 8 min 10.6 aL·min^{-1}; #6 as #4 but h = 20 s; for further explanation see main text

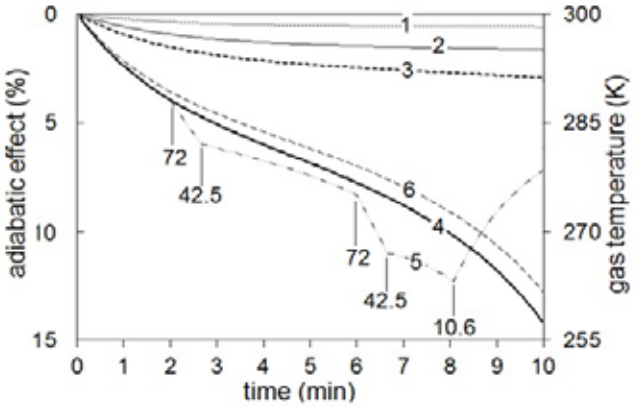
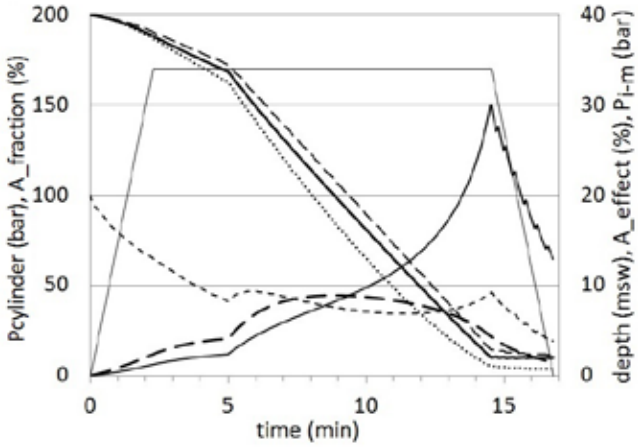


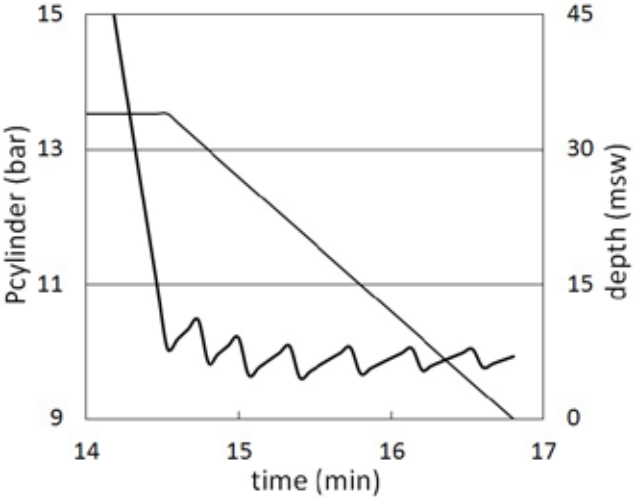
Figure 4

Model simulation starting with 17 aL·min^{-1} and, after 5 min, 42.5 aL·min^{-1} (water temperature 300 K, 12-L cylinder, 15 msw·min^{-1} descent and ascent speed, maximum depth 34 msw). Thin straight solid line, square profile (right axis); dashed curve, pure isothermal cylinder pressure (left axis); thick solid curve, cylinder pressure mixed process; stippled curve, pure adiabatic cylinder pressure, thin curve *A_effect* (right axis), thin stippled curve *A_fraction* (left axis), thick dashed line *AP_effect* (indicated by $P_{i\text{-}m}$)



adiabatic (*A_fraction* 100–65%). At the end of this dive, the isothermal and adiabatic components are nearly the same (Figure 4). In a cylinder pressure-versus-time diagram (as in Figure 4), this is apparent by comparing the isothermal, the adiabatic and the mixed-pressure curves with each other. The latter curve always lies in-between the two former curves. At the start, the mixed and adiabatic curves coincide (theoretically); during the dive the mixed curve creeps towards the isothermal one. During the ascent from square-wave dives and after leaving the MDD of a 'saw-tooth' dive, the

Figure 5
Cylinder pressure during the ascent from 34 msw; at t = 14.5 min, the blocking pressure of the first stage (10 bar) is reached and the emergency ascent starts; for further explanation see text



A_effect diminishes, unless the cylinder pressure approaches 10 bar, then, *A_fraction* (Figure 4) rises. *AP_effect* shows a flat maximum somewhere near the middle of the dive.

At 14.5 min total diving time, P_t = 10 bar, assumed to be the first-stage blocking pressure. However, theoretically it is possible to ascend by taking (sucking) breaths with well-controlled, long, slow expirations. The extra breathable air is provided by the temperature increase in the cylinder due to heat inflow from the surrounding water. Consequently the first-stage pressure supply becomes > 10 bar during the interval between inspirations. This additional air is proportional to the first-stage blocking pressure. In practice, the availability of spare gas is more complicated. For instance, the flow through the first stage is not a yes/no situation; the blocking pressure may decrease with ambient pressure and a rise in water temperature increases the warming up of the cylinder. Altogether, this may add a few minutes breathing time before complete 'shut off' of the air supply. This could represent the difference between surviving and drowning. In such an emergency situation, Figure 5 illustrates how from a depth of 34 msw theoretically one can make a controlled emergency ascent (ignoring stops).

OPEN-WATER DIVES

The dives (visibility ca. 35 m, negligible current, surface temperature 26.8–27.6°C, descent 23 m·min^{-1}, MDD 31–37 msw, temperature at MDD 22.5–25.6°C) were of low exertion, with an almost passive descent and, after leaving MDD, gas consumption was 17 aL·min^{-1} (≈ 2.5 METS; ≈ 9 mL O_2·kg^{-1}). Table 1 gives the modelled consumed gas mass (in mol) just before leaving MDD and the consumption calculated with the gas law on the basis of measured cylinder pressure and gas temperature (assumed to be the same as the water temperature) at the end of the buddy-breathing period. The difference is small (0.16%) and insignificant (paired Student's t-test, P = 0.25). If the release is assumed to be isothermal, then there is an overestimate of gas consumption. For the five dives this was on average 4.4 aL·min^{-1} during the descent (Table 1), about a quarter of the reference consumption of 17 aL·min^{-1}. At MDD the overestimate was about the same but after leaving MDD it slowly diminishes. At MDD the process was still predominantly adiabatic (*A_fraction* 80–90%).

Two dives performed in a pool at 4 metres' fresh water depth and with swimming speed of about 33 m·min^{-1}, the cylinder was emptied. The final adiabatic cooling was 60°C and *A_fraction*, initially falling, then increased to 31% by the end of the dive. After warming of the cylinder, the extra air supply was in accordance with the calculated amount, illustrating the above-mentioned principle of Figure 3.

Discussion

Adiabatic cooling of the gas in a diving cylinder during a dive results in an underestimate of the remaining gas supply. Adiabatic effects are not considered in commercially available dive computers. For a precise estimate of gas consumption during a dive, adiabatic effects on the cylinder gas should be taken into account as shown by modelling the adiabatic behaviour and by validating the model with actual dives. The adiabatic behaviour is complicated and

Table 1
Calculated and measured gas masses used for the descent and 2-min bottom stay of the five dives and overestimate of consumption during descent related to isothermal process

Dive	Modelled gas mass (mol)	'Measured' gas mass (mol)	Isothermal over-estimate consumption (aL·min^{-1})
D1	94.90	94.40	4.8
D2	89.89	89.69	3.4
D3	81.37	81.26	3.7
D4	88.16	88.20	6.0
D5	96.53	96.61	4.1
Mean (SD)	90.17 (6.01)	90.03 (5.97)	4.4 (0.9)

dependent on many parameters. Therefore, in some respects the modelling described has several weak points.

STUDY WEAKNESSES AND STRENGTHS

The derivation of Eq. [2] and applicability of a dive computer (Galileo) fulfils the aim of the study. The usefulness of Eq. [2] was established by the negligible difference in the modelled gas mass and the directly calculated gas mass after leaving MDD. A 50% increase of half time *h* resulted in an almost ten times larger deviation, indicating that the value of *h* used for 12-L aluminium cylinders filled with air (or nitrox) is realistic. However, a small error in *h* is acceptable (Figure 3, curve 6).

Part of the modelling was performed assuming a gas consumption of 42.5 aL·min^{-1} at 34 msw with bouts of 72 aL·min^{-1}. The question arises whether this is realistic. Taking 180 aL·min^{-1} at atmospheric pressure as the 15 s maximal voluntary ventilation (MVV15), $MVV15_{34msw} = 180p^{-0.4} = 96$ aL·min^{-1}; (where p is absolute pressure (bar)).[2] This is a conservative estimate; after a 9-min, 200-watt load at 36 msw an MVV15 of 160 aL·min^{-1} has been reported.[3] The sustained MVV was not given, but one should need about 38 aL·min^{-1} (extrapolated from sustained MVV exercise data). At sea level in air, the sustained MVV (> 4 min) is between 60 and 90% of MVV15.[4–6] We conclude that the consumption of 42.5 aL·min^{-1} is about 65% of $MVV15_{34msw}$ and allows heavy work; swimming speed 27 m.min^{-1} (calculated from ref. 7, ventilation/$\dot{V}O_2$ conversion factor 25; body mass 70 kg; close to thermal equilibrium).[7] The above shows that the chosen gas consumption rates are realistic assuming a diver's high level of fitness ($\dot{V}O_{2max}$ > 40 mL.kg^{-1}.min^{-1}). With cold stress (TW dive of Figure 2), which requires some 8 aL·min^{-1} extra (calculated from ref. 8), 25 aL·min^{-1} is needed,[8] whereas the swimming speed is subjectively very low (approximately 10 m.min^{-1}).

A disputable point is the practical value of the 'extra adiabatic' spare gas in an 'out-of-air' situation. Only specific training in breathing control under safe conditions (deep pool, etc.) would increase the chances of survival.

By implementing the method in dive computers, a realistic estimate of the instantaneous gas consumption can be obtained during a dive. For a precise correction during the descent, the water temperature sensor-technology should preferably have a half time < 10 s. An initially non-equilibrated cylinder gives an error in the consumption (about $100\Delta T/T_{water}$% with ΔT water-cylinder temperature difference) that fades away with the half time *h*. In practice, this is a minor drawback. Another inaccuracy, the gas needed to equalize the lung, etc., and to inflate the BCD, can be corrected for with a simple algorithm (by using biometric data and suit thickness). Another algorithm can adjust *h* for cylinder size and material, and the consumption level (via a feedback). Summarising, a high quality DC with the above features is an adequate device to perform the adiabatic correction.

DEPENDENCY ON CONDITIONS AND APPLICATION

The evolution of *A_effect* and *A_fraction* is complicated since they are strongly dependent on depth and the diver's gas consumption (level of exercise; compare 10L with LC curve in Figure 2). Therefore, general 'rules' can hardly be given. Increasing cylinder volume decreases A_effect substantially (Figure 2). High versus low water temperature (compare 12-L with 4^{o}C curve in Figure 2) and changes in water temperature during the dive are of minor importance. All the curves of Figure 2 have similar shapes. They coincide well after axis transformation in both directions. However, the major phenomenon is the decrease of *A_ratio* and increase of *A_effect* up to a cylinder pressure of some tens of a bar. For lower pressures, the effect may reverse. Generally, *AP_effect* has a flat maximum at 5–10 bar somewhere near the middle of the dive.

The descent is the most prominent part of the dive with respect to the adiabatic correction that can amount to more than 5 aL·min^{-1}. The increase in depth is the major cause. With a saw-tooth profile (the open-sea dives) the correction becomes progressively less important after leaving MDD. Finally it diminishes to some percent of the gas supply of the cylinder just before surfacing. These results for saw-tooth-like profiles strongly contrast with those of square profiles where adiabatic cooling at the start of the ascent can be many tens of degrees. However, the adiabatic effect diminishes less with a low swimming speed since *h* increases with decreasing swimming speed, resulting in stronger adiabatic behaviour.

In diving history, especially recreational diving, fatalities are not always well explained. Even nowadays, divers descend in two minutes to some 50 m depth on air. Sometimes a fatality happens shortly after the descent. Consumption calculations during the descent, that generally have large overestimates when not corrected, can shed light on the cause of the fatality (e.g., hypercapnia). In other cases there may have been a high consumption at great depths in combination with a low water temperature. Then, the low gas temperature resulting from adiabatic cooling might have caused blockage of the regulator (plastic components) due to freezing, resulting in the calamity. (With 4^{o}C water temperature, 34 aL·min^{-1} and 12-L cylinder, within 72 s the gas temperature cools to -2^{o}C (Figure 2). For such dives, the adiabatic correction after DC data retrieval gives a better reconstruction of actual gas consumption. However, in general, the adiabatic correction has a limited value for forensic aims or accident reconstruction. In cardiorespiratory physiological research the actual gas consumption gives a more complete view of the physiology during the dive.

Conclusions and recommendations

In this study, model parameters were validated by means of pressure measurements during actual dives. The theoretical analyses show that even with moderate gas flows, the adiabatic correction is relevant when aiming to closely follow the evolution of the gas content of a cylinder. This holds especially for the descent and for deep, square-wave dives (> 30 msw). Moreover, the model shows that decreasing cylinder volume and increasing the gas flows strongly increases the adiabatic effect. Both the modelled and actual dives with a saw-tooth profile indicate that, with low exertion, the adiabatic effect is restricted to about 4% near the end of the dive. Square-wave dives give the largest effect; at the moment that a cylinder pressure of 50 bar is reached, the effect is about 9% and with 'out of air' > 20%. After high pulmonary ventilation, 'out of air' means there is still some reserve that enables the diver to reach the surface, due to the substantial adiabatic effect that has cooled the gas in the cylinder. It is recommended that managing an 'out of air' situation is a subject in diving education.

The developed method seems sufficiently accurate for research and for specific cases of fatality reconstruction and is implementable in DCs. Unfortunately in practice, accuracy does not hold for temperature recording by DCs due to the long half time of the sensor technology and its strong dependency on current (swimming speed). In contrast, cylinder pressure is measured accurately and without delay. However, due to the adiabatic effect it does not allow an accurate extrapolation to the remaining gas supply. As a result, it gives an underestimate of the remaining bottom time, a quantity provided by some modern DCs. The 'extra' gas with an out-of-air, heavy exertion deep dive can be considered as a beneficial side effect of a DC that actually fails to correct for the adiabatic effect. The adiabatic effect can be minimized for cold water diving by an optimal choice of cylinder size; for most recreational diving, a 12-L aluminium cylinder is suitable. The cylinder should be mounted as freely as possible in the BCD to facilitate heat inflow.

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Acknowledgements

The authors thank Harry J van Grol for developing a model to calculate the heat transfer and Jochen Schipke for suggestions to improve the manuscript.

Conflict of interest: nil

Submitted: 11 June 2015; revised 01 October 2015
Accepted: 04 October 2015

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Economic outcomes in clinical studies assessing hyperbaric oxygen in the treatment of acute and chronic wounds

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Abstract

(Santema TB, Stoekenbroek RM, van Steekelenburg KC, van Hulst RA, Koelemay MJW, Ubbink DT. Economic outcomes in clinical studies assessing hyperbaric oxygen in the treatment of acute and chronic wounds. *Diving and Hyperbaric Medicine*. 2015 December;45(4):228-234.)

Introduction: Hyperbaric oxygen treatment (HBOT) is used to treat acute and chronic wounds. This systematic review was conducted to summarise and evaluate existing evidence on the costs associated with HBOT in the treatment of wounds.

Methods: We searched multiple electronic databases in March 2015 for cohort studies and randomised clinical trials (RCTs) that reported on the clinical effectiveness and treatment costs of HBOT in the treatment of acute or chronic wounds.

Results: One RCT and three cohort studies reported on economic as well as clinical outcomes. These studies comprised different disorders (ischaemic diabetic foot ulcers, thermal burns, Fournier's gangrene and necrotising soft tissue infections) and employed different clinical and economic outcome measures. Only the RCT had a good methodological quality. Three of the included studies reported that their primary clinical outcomes (wound healing, hospital stay, complications) improved in the HBOT group. The effects of HBOT on costs were variable.

Conclusions: Currently, there is little direct evidence on the cost-effectiveness of HBOT in the treatment of acute and chronic wounds. Although there is some evidence suggesting effectiveness of HBOT, further studies should include economic outcomes in order to make recommendations on the cost-effectiveness of applying HBOT in wound care.

Key words

Hyperbaric oxygen therapy; wounds; outcome; cost-effectiveness; systematic review

Introduction

Chronic and acute wounds pose a major healthcare problem and put a substantial burden on the healthcare budget. In the United Kingdom, approximately £2.3–3.1 billion or 3% of the total National Health Service (NHS) budget, is spent annually on the treatment of chronic wounds.[1] Therefore, the evaluation of the cost-effectiveness of established and novel treatment options for such conditions is of great importance. Wounds can result from surgery, trauma or underlying diseases such as diabetes, venous insufficiency or peripheral arterial disease. During normal wound healing, anatomical and functional integrity will be restored. However, normal wound healing can be disrupted and healing subsequently delayed. If wounds do not adequately heal with standard wound care (e.g., infection control, wound dressings, foot care education), more advanced wound care treatments can be considered, such as hyperbaric oxygen.

Hyperbaric oxygen treatment (HBOT) is currently used in the treatment of acute and chronic wounds, such as diabetic foot ulcers, radiation injury and necrotising fasciitis.[2–5] HBOT regimens for the treatment of wounds typically involve repeated sessions of 60 to 120 minutes in a compression chamber with a pressure between 203 and 304 kPa. During the session, the patient inhales 100% oxygen through a mask. Tissue oxygenation is improved mainly as a result of the increased driving partial pressure into tissues caused by HBOT. Furthermore, angiogenesis may be stimulated due to the promotion of oxygen-dependent collagen matrix formation and the mobilisation of stem cells by oxidative stress and their role in wound healing.[6,7]

Multiple review articles have reported on clinical outcomes of HBOT in wound treatment, with mixed results.[2,3,8,9] However, the economic aspects were not considered in these review articles. Yet cost-effectiveness is of key importance in evaluating the benefit of implementing interventions in practice,[10] particularly regarding a time-consuming treatment option like HBOT. This systematic review was conducted to evaluate existing evidence on the costs associated with HBOT in the treatment of acute and chronic wounds in clinical studies and to guide clinical decision-making and further research on this topic.

Methods

We performed a systematic review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.[11]

SEARCH STRATEGY

A comprehensive review of the literature was performed to identify all studies that evaluated both the clinical effectiveness and the economic impact of HBOT in the treatment of acute and chronic wounds published up to March 2015. The searched databases included MEDLINE, EMBASE, The Cochrane Central Register of Controlled Trials (CENTRAL), the NHS Economic Evaluation

Table 1
Flow chart of study inclusions and exclusions

References identified and screened for retrieval after removing duplicates (n = 1,040)
↓
Not eligible based on title and abstract (n = 1,018)
↓
Full-text articles retrieved for more detailed evaluation (n = 22)
↓
Not eligible based on full text (n = 18)
– no economic assessment (n = 9)
– no original study data (n = 7)
– no HBOT (n = 2)
↓
Included studies (n = 4)

Database and the Health Economic Evaluations Database (HEED). A clinical librarian assisted in formulating an appropriate search strategy. Medical Subject Headings (MeSH) terms were used in combination with key terms and their synonyms such as 'wounds', 'hyperbaric oxygen', 'HBOT' and 'costs'. Additional publications were identified by reviewing the reference lists of retrieved studies. No language restrictions were applied.

SELECTION OF INCLUDED STUDIES

Eligible studies were either cohort studies or randomised clinical trials (RCTs) that reported on both the clinical effectiveness and treatment costs of HBOT. Furthermore, eligible RCTs should deal with the treatment of open wounds of any type and aetiology, including soft tissue infections. Only studies that compared HBOT with standard care or placebo treatment were included in this study. RCTs on the topical application of HBOT were excluded. Two of the authors (TS and RS) independently screened titles and abstracts of potentially eligible studies. Subsequently, full-text versions of these publications were retrieved.

ASSESSMENT OF STUDY QUALITY

The risk of bias and methodological quality of the included studies was assessed by two review authors (TS and RS) using the Downs-Black instrument and the Drummond checklist.[12,13] The Downs-Black instrument is validated for the assessment of quality of randomised and non-randomised studies and consists of 27 items categorised in five subscales. These subscales are divided into the themes 'reporting' (10 items), 'external validity' (three items), 'bias' (seven items), 'confounding' (six items) and 'power' (one item). The maximum total score using the original instrument is 32, but we modified the score for the items 'confounding' and 'power'. The original scale ranged from 0 to 2 for 'confounding' and 0 to 5 for 'power', but we changed these items into dichotomous variables (i.e., scoring '1' if a power or sample size calculation was present and '0' if not). Each study could therefore score a maximum of 27 points on the modified Downs-Black instrument.

The Drummond checklist is a tool for the assessment of quality of the economic evaluation conducted alongside a clinical effectiveness study and consists of 35 items categorised in three subscales. These subscales are 'study design', 'data collection' and 'analysis and interpretation of results'. Scores that can be obtained for each item are, 'yes', 'no', 'not clear' and 'not appropriate'. We recoded these scores into dichotomous variables, 'yes' scoring '1' and 'no' or 'unclear' scoring '0'. Because no meta-analyses were included in this review, one item was not applicable to the studies. The maximum score could therefore be 34 (instead of 35) on the Drummonds checklist.

DATA COLLECTION AND EXTRACTION

Data extraction was performed by the same two authors independently using a standard extraction form. Extracted study information included research design and setting, year of publication, inclusion criteria, number of included participants, method of allocating patients, details about the HBOT therapeutic regimen and treatment in the control group, clinical outcome measures, and economic outcome measures, as defined by the authors of the papers. Discrepancies were resolved by discussion among the review authors.

DATA ANALYSIS

For dichotomous outcomes, differences between treatment groups are expressed as risk differences (RD) and numbers needed to treat or harm (NNT or NNH), along with their 95% confidence intervals (CIs). For continuous outcomes, differences are expressed as mean differences (MDs), along with 95% CIs. We planned to do a meta-analysis only in case of limited clinical and statistical heterogeneity (i.e., if the I^2 was less than 50%).

Results

The initial search identified 1,040 potentially relevant publications. Full-text articles were retrieved for 22 publications which were deemed potentially eligible based on their titles and abstracts. Eighteen of these articles were subsequently excluded. Reasons for exclusion are shown in Table 1. Eventually, only four articles were considered eligible for inclusion in this review.

STUDY CHARACTERISTICS

The four included studies comprised various categories of patients. Abidia et al. performed a RCT which included 18 patients with ischaemic diabetic foot ulcers.[14] Cianci et al.

Table 2
Characteristics of included studies; HBOT – hyperbaric oxygen treatment; * – not specified

Study	**Abidia et al**[14]	**Cianci et al**[15]	**Mindrup et al**[16]	**Soh et al**[17]
Wound type	Ischaemic diabetic foot ulcers	Thermal burns	Fournier's gangrene	Necrotising soft tissue infections
Study design	Randomised trial	Prospective cohort	Retrospective cohort	Retrospective cohort
Country	UK	USA	USA	USA
Participants (*n*)	18	21	42	45,913
- HBOT group	9	10	26	405
- control group	9	11	16	45,508
HBOT sessions				
- Total sessions	30	*	2–26 (median 6)	*
- Duration	90 minutes	90 minutes	30–90 minutes	*
- Pressure (kPa)	243	203	243–304	*
Control treatment	Sham HBOT	Standard treatment	Standard treatment	No HBOT
Follow-up period	1 year	13–81 days	9 months–10 years	*

Table 3
Quality assessment using the Downs and Black instrument

Study	**Abidia et al**[14]	**Cianci et al**[15]	**Mindrup et al**[16]	**Soh et al**[17]
Reporting				
Objective	+	+	+	+
Main outcomes	+	+	+	+
Patient characteristics	+	+	+	+
Intervention	+	–	+	–
Confounders	+	+	+	–
Main findings	+	+	+	–
Variability	+	–	+	–
Adverse events	+	–	–	–
Loss to follow-up	+	–	–	–
Probability values	+	–	+	+
External validity				
Representative subjects invited	+	–	–	–
Representative subjects participated	+	–	–	–
Representative treatment	+	+	+	+
Internal validity – bias				
Blinding subjects	+	–	–	–
Blinding outcome assessors	+	–	–	–
Data dredging	+	+	+	–
Length of follow up	+	–	–	–
Statistical tests	+	–	+	+
Compliance	+	–	–	+
Accurate main outcome measures	+	+	+	+
Internal validity – confounding				
Selection bias	+	–	+	+
Period of time	+	–	+	+
Randomisation	+	–	–	–
Concealment	+	–	–	–
Confounding	+	–	–	–
Loss to follow up	+	–	–	–
Power				
Sample size	–	–	–	–
Total score	26/27	8/27	14/27	10/27

Table 4
Quality assessment using the Drummond checklist; * only original clinical studies are included in this review, so this item is not applicable

Study	Abidia et al[14]	Cianci et al[15]	Mindrup et al[16]	Soh et al[17]
Study design				
Research question	–	+	–	–
Economic importance	–	+	–	–
Viewpoint(s) of the analysis	–	–	–	–
Rational alternative treatment	–	–	–	–
Alternative treatment	+	–	–	–
Form of economic evaluation	–	–	–	–
Form justified	–	–	–	–
Data Collection				
Sources	+	+	+	+
Design	+	+	+	+
Meta-analysis	*	*	*	*
Primary outcome	±	–	–	–
Value benefits	–	–	–	–
Subjects	–	–	–	–
Productivity	–	–	–	–
Relevance productivity	–	–	–	–
Resource use	–	–	–	–
Estimation quantities	±	–	–	–
Currency and prize data	±	–	–	–
Inflation	–	±	±	±
Model	–	–	–	–
Model justified	–	–	–	–
Analysis and interpretation of results				
Time horizon	+	–	–	–
Discount rate	–	–	–	–
Choice of rate	–	–	–	–
Explanation if not discounted	–	–	–	–
Statistical tests for stochastic data	–	–	–	–
Sensitivity analysis	–	–	–	–
Choice of variables	–	–	–	–
Ranges variables	–	–	–	–
Alternatives	–	–	–	–
Incremental analysis	–	–	–	–
Disaggregated and aggregated	–	–	–	–
Answer study question	–	–	–	–
Conclusion from data reported	–	–	–	–
Conclusions with caveats	–	–	–	–
Total score	4/34	4/34	2/34	2/34

included 21 patients with thermal burns in a prospective cohort study.[15] The retrospective cohort study by Mindrup et al. included 42 patients with Fournier's gangrene.[16] The retrospective study by Soh et al. described a cohort of 45,913 patients with necrotising soft tissue infections (NSTIs) taken from the United States Nationwide Inpatient Sample.[17]

HBOT therapeutic regimes, as well as treatment pressure and session duration, were quite different among the studies. Only Abidia et al. employed sham HBOT with 100% oxygen in the control group, while other studies compared HBOT to wound care without HBOT.[14] A complete overview of the study characteristics is shown in Table 2.

METHODOLOGICAL QUALITY

The methodological quality of the RCT by Abidia et al. was very good (26 out of 27 points).[14] The observational nature of the other studies limited their validity, which is reflected by their relatively low scores on the Downs and Black quality assessment tool (Table 3). The quality of the economic evaluations was poor in all four studies. This is reflected by lower scores on the Drummonds checklist (Table 4).

Table 5
Primary clinical outcomes; CI – Confidence interval; HBOT – Hyperbaric oxygen treatment; MD – mean difference; NNT – number needed to treat; RD – risk difference; * not applicable

Study	**Abidia et al**[14]	**Cianci et al**[15]	**Mindrup et al**[16]	**Soh et al**[17]
Main outcome	Ulcers healed after one year	Length of hospital stay (days)	Disease specific mortality	In-hospital mortality
HBOT group	5/9	Mean 28.4 (range 13–60 ± 16.1)	7/26	18/405
Control group	0/9	Mean 43.2 (range 20–81 ± 19.4)	2/16	4,289/45,508
RD (95% CI)	56% (22 to 89%)	MD 14.8 (-1.6 to 31.2)	-14% (-36 to 13%)	47% (30 to 74%)
NNT (95% CI)	NNT 2 (1 to 5)	*	*	20 (15 to 50)

Table 6
Primary economic outcomes; CI: confidence interval; HBOT: Hyperbaric oxygen treatment; * statistically non-significant; † average daily hospital charges were statistically higher in the HBOT treated group

Study	**Abidia et al**[14]	**Cianci et al**[15]	**Mindrup et al**[16]	**Soh et al**[17]
Main outcome	Costs of treatment per year	Costs of burn care	Total hospital charges	Hospitalisation costs
Monetary unit	GBP	USD	USD	USD
HBOT group	Mean 4,972	Mean 60,350 (± 9,250)	Median 63,199 (range 31,858–256,741)	Median 52,205 (95% CI 46,397–58,012)
Control group	Mean 7,946	Mean 91,960 (± 12,590)	Median 51,185 (range 8,691–$427,283)	Median 45,464 (95% CI 44,7867–46,060)
Cost benefit?	37% cost reduction	34% cost reduction*	23% cost increase*†	15% cost increase

CLINICAL OUTCOMES

Three of the included studies reported that HBOT positively affected clinical outcomes (Table 5). The RCT by Abidia et al. demonstrated improved healing of ischaemic diabetic ulcers at one year of follow-up.[14] Cianci et al. reported a reduced length of hospital stay in HBOT-treated patients with thermal burns.[15] Soh et al. reported a longer length of hospital stay, but lower complications and in-hospital mortality in patients with NSTI who were treated with HBOT.[17] Nevertheless, Mindrup et al. demonstrated a non-significant increase in disease-specific mortality among patients with Fournier's gangrene who received HBOT.[16]

ECONOMIC OUTCOMES

The depth of the economic analyses varied widely among the four included studies. An overview of all economic outcome findings is shown in Table 6.

Abidia et al. assessed the costs of hospital visits for wound care and HBOT costs during the one-year follow-up period using unit costs as obtained from the NHS (*pounds sterling,* £) £58 for an outpatient visit and £100 for an HBOT-session), and reported lower overall costs in HBOT-treated patients (£4,972 vs. £7,946).[14] The extra costs for HBOT were compensated by a substantial reduction in the number of outpatient visits (33.75 visits in the HBOT group vs. 136.5 in the control group).

Cianci et al. reported a non-significant reduction in the costs of hospitalisation for HBOT-treated patients by reviewing all hospital bills.[15] The authors corrected the costs of inflation by standardising prices to 1987 levels but did not use appropriate statistical tests for non-parametric cost data.

In the study by Mindrup et al. the primary economic outcome was the total hospital costs.[16] Median total hospital costs were higher in the HBOT group, but this difference was not statistically significant (median costs USD $63,199 vs. $51,185). However, they reported statistically significant higher average daily hospital expenditures for HBOT-treated patients ($3,384 vs. $2,552) compared with non-HBOT treated patients.

Also, in the retrospective cohort study by Soh et al., the main economic outcome parameter was the total hospital charges during hospitalisation.[17] After adjustments for inflation, the authors reported statistically significantly higher median hospital costs in the HBOT group.

Discussion

This systematic review demonstrates that there is little direct evidence on the cost-effectiveness of HBOT in the treatment of chronic or acute wounds. Only four clinical studies were found that reported clinical as well as economic outcomes. Each study comprised of patients with different wound types, which prevented pooling of the results. Furthermore, outcome measures were very heterogeneous for both clinical and economic endpoints. Moreover, the economic analyses were of limited quality, failed to include an in-depth analysis, and were conducted in different decades.

A number of recent systematic reviews have reported on the clinical effectiveness of HBOT for patients with chronic ulcers or late radiation tissue injury.[2–4] Most of these reviews focussed on patients with diabetic ulcers and were hampered by between-study heterogeneity and limited methodological quality. Nevertheless, there is some evidence on the effectiveness of HBOT in improving the healing of diabetic foot ulcers and late radiation tissue injury.[3,4] Also, some evidence exists on the effectiveness of additional HBOT for acute wounds.[9]

Given the magnitude of the health problem and its economic impact, evidence for cost-effective treatments is essential in wound care. Prospective clinical studies are required to accurately assess cost-effectiveness, as all relevant and important clinical and cost parameters must be measured simultaneously. Although an economic analysis is rarely the primary purpose of a clinical study, a few adjustments to the study design can ensure that the data can be used in high-quality economic analyses.

None of the included trials in this review stated which economic perspective was taken into account. When performing a cost-effectiveness analysis alongside a clinical trial, the most preferred approach is taking all costs into account from a societal perspective. After this analysis, the perspective can be changed into the standpoint of, e.g., the government, the hospital or the patient.[13]

A cost-utility analysis is the preferred option when a study aims to determine the costs and efficacy of a treatment option, in which quality of life is an important factor. In such analyses, the outcome is often expressed as the effect on the quality-adjusted life years (QALY) that are lost or gained by the use of a specific therapy.[13] The International Society for Pharmacoeconomics and Outcome Research Task Force in Good Research Practices: randomized clinical trials–cost-effectiveness analysis (ISPOR RCT-CEA) has formulated recommendations for the design of economic analyses alongside clinical trials.[18] An important recommendation is that health utilities or QALYs should be measured directly from the study participants. Health utilities are preference-weighted health states on a scale from 0 (death) to 1 (perfect health) that can be measured by using utility questionnaires such as the EuroQol-5D.[19,20] Unfortunately, none of the included studies in the present review measured utilities or expressed their health outcomes as QALYs.

Besides clinical studies assessing economic outcomes, a few economic evaluations have been performed. The results of such evaluations are highly dependent on specific assumptions on treatment costs and clinical outcomes. An example of this kind of evaluation is a budget impact study in which a decision model comparing additional HBOT with standard care alone in the treatment of diabetic foot ulcers was developed.[21] This model included only the costs of the HBOT. Efficacy data were obtained from a review of clinical studies that were of poor methodological quality. They concluded that over a 12-year period, the costs for the treatment of patients with diabetic foot ulcers with HBOT would be lower than the costs for standard care alone in the Canadian setting (CND $40,695 vs. $49,786).

An example of an ongoing clinical trial on HBOT in wound care is the Dutch DAMOCLES trial. The objective of this clinical trial is to investigate the cost-effectiveness of HBOT in patients with ischaemic diabetic ulcers. In the DAMOCLES trial, all medical and direct non-medical costs are assessed and QALYs are measured.[22]

Conclusions

Although HBOT seems effective for various acute and chronic wounds, the lack of available evidence on economic endpoints is striking, given the fact that HBOT is widely applied in these settings and is reimbursed by insurance companies in Europe and the USA for the treatment of chronic wounds. Future research should include economic outcomes in large clinical studies of strong methodological quality to ensure that meaningful results can be used in clinical decision making and economic evaluations.

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Acknowledgements

The authors thank Rene Spijker, clinical librarian, for his assistance in performing the literature search.

Conflict of interest: nil

Submitted: 20 March 2015; revised 10 June and 10 November 2015
Accepted: 22 November 2015

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The database of randomised controlled trials in hyperbaric medicine maintained by Michael Bennett and his colleagues at the Prince of Wales Hospital Diving and Hyperbaric Medicine Unit, Sydney is at: <http://hboevidence.unsw.wikispaces.net/>

Assistance from interested physicians in preparing critical appraisals is welcomed, indeed needed, as there is a considerable backlog. Guidance on completing a CAT is provided.
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Review article

The aging diver: endothelial biochemistry and its potential implications for cardiovascular health

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Abstract

(Berenji Ardestani S, Buzzacott P, Eftedal I. The aging diver: endothelial biochemistry and its potential implications for cardiovascular health. *Diving and Hyperbaric Medicine*. 2015 December;45(4):235-239.)

Divers are exposed to circulatory stress that directly affects the endothelial lining of blood vessels, and even asymptomatic dives are associated with inflammatory responses, microparticle release and endothelial dysfunction. As humans age, there is a relative increase in the risk of cardiovascular disease, attributed in part to declining endothelial function. Whether extensive diving in the older diver increases the risk of disease as a result of accumulated circulatory stress, or provides protection through processes of acclimatization remains an open question. We provide a brief review of current knowledge about the separate effects of diving and aging on the vascular endothelium in humans and rodents, and discuss the available data on their combined effects. The aim is to elucidate possible outcomes of the interplay between exogenous and endogenous stress factors for endothelial function and to question potential implications for cardiovascular health in the aging diver.

Key words

Age; diving; cardiovascular; endothelium; stress; free radicals; review article

Introduction

Diving with compressed gas is associated with circulatory stress that affects the cardiovascular system, characterized by altered redox status, activation of inflammatory signalling, microparticle release and a transient dysfunction of the vascular endothelium.[1–5] Any resulting health effects will conceivably depend on individual traits of the diver, including age.[6] There is evidence that the recreational diving population may be aging,[7,8] whilst occupational divers may continue their careers as long as they pass their annual medical examination.

The cardiovascular system undergoes complex phenotypical and functional changes with aging. Age-dependent decline of endothelial function comes as a consequence of increased biochemical stress and results in a gradual progression towards a pro-inflammatory and atherosclerotic phenotype.[9] Whether this is further aggravated by transient stress from diving remains an open question. The contrary may also be the case, with regular diving triggering protective acclimatization.

In this article, we provide a summary of current knowledge about the biochemical effects of diving and aging, separately and combined, on the vascular endothelium, and discuss them in light of cardiovascular health data. The aim is to elucidate possible outcomes of the interplay between exogenous and endogenous stress on vascular endothelial function using data from both human and rodent studies and to discuss the potential implications for cardiovascular health in aging divers.

Biochemistry of the vascular endothelium

The vascular endothelium is a key regulator of vascular homeostasis.[10] Its function is mediated via the production and release of vasoactive molecules, first described in 1980 and termed acetylcholine-induced endothelium-derived relaxing factors (EDRF).[11] EDRFs regulate the diameter, structure and tone of the vasculature, thereby balancing oxygen supply with the metabolic demands of neighbouring tissues. It was later determined that the essential EDRF was the free radical nitric oxide (NO).[12,13] NO is derived from the amino acid L-arginine by nitric oxide synthase (NOS)-driven catalysis. In the endothelium, NO production is catalyzed by endothelial nitric oxide synthase, eNOS.[14,15] Shear stress generated by flowing blood activates eNOS in healthy vessels and the resulting NO has EDRF function.[16]

Under normal physiological conditions, NO is the sole catalytic product of eNOS. However, when intracellular oxidative stress from exogenous or endogenous sources increases, a switch in eNOS activity may occur, resulting in production of the reactive oxygen species superoxide (O_2^-). Enzymatic conversion of O_2^- by superoxide dismutase produces hydrogen peroxide (H_2O_2). H_2O_2 is highly diffusible and can cause injury to endothelial cells. Also, the interaction of O_2^- with NO generates the reactive nitrogen species peroxynitrite ($ONOO^-$), which inactivates the essential eNOS cofactor tetrahydrobiopterin (BH4). The net result is a loss of eNOS activity followed by endothelial activation and ultimately by endothelial dysfunction. The failure to uphold vascular homeostasis is accompanied by elevated levels of circulating cytokines, intravascular platelet aggregation and inflammation in the surrounding

tissue.[17] Endothelial dysfunction occurs in a number of cardiovascular diseases, e.g., atherosclerosis and coronary artery disease, the risks and progression of which are linked to the severity of endothelial dysfunction.[18]

Diving impairs endothelial function

The dynamics of inert gas uptake and elimination during diving add to the physical stress from the hyperbaric environment such that, even in healthy divers, circulatory stress in the form of transient endothelial dysfunction, inflammatory responses and microparticle release are observed following routine dives.[1–4,19] Although no direct correlation between the symptoms of decompression sickness (DCS) and bubbles has been found, DCS risk increases with increasing bubble loads.[20]

It has been hypothesized that a transient loss of vascular homeostasis in response to altered redox status is the underlying cause of DCS, with bubbles acting as an exacerbating factor.[21] Suggested pathophysiological mechanisms linking bubbles to DCS development include direct physical injury to the vascular endothelium, as reported in the pulmonary aorta of pigs after simulated air dives,[22] and biochemical processes, as indicated by complement activation in human serum infused with air bubbles.[23]

Aging is associated with declining endothelial function

The gradual decline in vascular endothelial function towards a pro-inflammatory and atherosclerotic phenotype starts in childhood, with clinical symptoms typically appearing in middle age.[12,24,25] This deterioration with age, even in individuals who are not at particular risk for cardiovascular disease, predisposes both sexes to ischaemic heart disease,[26] though men experience earlier and more severe atherosclerosis than women. Middle-aged men have been shown to have a five-fold higher risk than women of dying from cardiovascular disease.[27] Both clinically evident and occult cardiovascular disease increase with age,[28] and this may be a factor to consider for elderly participants in physically demanding activities such as diving.

Comparative observations from rodents

The use of animal models in diving research allows for control of environmental and biological factors that might otherwise confound the outcome and for a more liberal use of protocols that lie outside of the boundaries for safe human diving, in order to provoke pathological responses. Studies of diving-related pathology in rodents often use non-invasive measures that are assumed to correlate to human symptomatology. DCS is typically inferred either from post-dive behavioural changes,[29] or from measurements of decompression-induced bubble loads in the circulation.[30,31] The endothelial dysfunction seen in healthy humans after air dives also appears to occur in both rodents and rabbits.[32,33] The endothelial responses are likely triggered by oxidative stress, as indicated by observed redox-dependent gene expression changes in rat aorta after simulated dives.[32] Also of interest is the potential acclimatization to diving. Rats dived daily on low-stress air profiles have reduced mortality and fewer signs of neuronal impairment after a single provocative dive than their naïve controls.[34] Taken together, these observations support the role of exogenous oxidative stress in the cardiovascular pathophysiology of diving, and the prospect of injury prevention through control of oxidative stress levels.

Rats are also used in comparative studies of cardiovascular aging. Some hallmarks of vascular aging are similar in humans and rats, such as remodelling of the arterial wall, with thickening of the intima-media, vascular stiffening and endothelial dysfunction.[28] Atherosclerosis is normally not seen in rats,[35] but some strains exist in which atherosclerosis develops in response to high cholesterol diets, or as a consequence of targeted genetic modifications (as in the apoE knockout).[36] A severe reduction of flow-induced relaxation in response to increased shear stress has been demonstrated in isolated coronary arterioles of approximately 80-week-old rats (corresponding to a human age of 65 to 70 years).[17] This appears to be related to perturbations in NO metabolism in the vessel wall, that indicate that the aged cells lose their ability to increase NO synthesis even in the presence of abundant substrate. The aging rats also have higher generation of O_2^- in their coronary vessels at basal conditions compared with young controls, consistent with the biochemical changes of the vascular endothelium in aging humans.

The aging diver: at risk or protected?

Thus, the aging diver's circulatory system is simultaneously exposed to both transient exogenous stresses from the hyperbaric environment and age-related functional decline of factors that maintain vascular homeostasis. The central question is whether the net effect for the individual diver is detrimental or beneficial for cardiovascular health.

Younger divers produce fewer bubbles than older divers.[6] A decrease of $\dot{V}O_{2max}$ and increased adiposity with increasing age has been postulated to be the main reason for these changes.[6] More recently a positive relationship between age and post-dive bubbles has been reported, as well as the level of post-dive bubbling being both significantly higher in males than in females and associated with weight and body fat mass.[38] In another study, bubble loads in divers were significantly associated with increasing age and decreasing estimated $\dot{V}O_{2max}$, but not with percentage of body fat.[39] However, the correlation between bubble grade and probability of DCS is not close, and the limited epidemiological data available are also conflicting.

The risk of DCS among insured members of the Divers Alert Network (DAN) during the period 2000–2007 peaked at age 35–45 years with 27 cases per 10,000 member-years, then falling to just 16 cases per 10,000 member-years by age 60–69.[7] Reasons for this may be less physiological than behavioural; for example, if divers dive more cautiously as they age. Between 1992 and 2003, the mean age of DAN members increased by one year every four years, whereas the mean age of diving fatalities over the same period increased by two years every four years.[40] The percentage of cardiac-related factors among these diving fatalities increased from less than 5% before age 35 years to 30% from age 50 years onward.[40] Whereas the mean age of diving fatalities in 1992 was about two years older than for DAN members as a whole, by 2003 the mean age of DAN members had risen from 37 to 41 years and the mean age of diving fatalities to 46 years suggesting a greater fatality rate amongst older divers.[40]

Reports of cardiovascular-related death among divers indicate that cardiovascular fatalities peak in the 50- to 60-year age range. Among 947 fatalities in recreational divers, 26% were related to cardiac incidents associated with a history of cardiac disease or age greater than 40.[41] Being male and over 50 is recognized as the principle predictor of non-congenital cardiac incidents in divers. The association with male sex is also seen in younger individuals; the relative risk of cardiovascular mortality in male divers over 30 is six times greater than that of female divers of the same age.[8]

While physical activity in itself provides cardio-protection, diving may offer additional benefit through acclimatization to oxidative stress. Indications of acclimatization to hyperbaric exposure were first seen in caisson workers, where the incidence of DCS was reported to fall markedly over a period of two to three weeks of compressed air work; the effect being lost after off-work breaks of two to 10 days.[42]

The idea was further strengthened in a retrospective study of occupational divers performing repetitive, daily air dives, in whom DCS was treated most frequently early in the period.[43] Biological indications of acclimatization to diving were later reported in a cohort of military diving trainees.[44] There were no incidences of DCS or other medical problems, but there were significant changes in several biomarker levels, leading to the conclusion that extensive diving activates defensive acclimatization towards inflammatory insults.[44]

On an even more basic level, signs consistent with acclimatization to diving have also been observed in the gene expression patterns of peripheral leukocytes from experienced, male divers.[2] Stable changes in the activity of genes involved in apoptosis, inflammation and innate immunity persisted for two weeks after their last dive, consistent with defence against the augmented oxidative stress to which they had been repeatedly exposed during their diving careers.

Limitations to our understanding

Aging divers may include unfit individuals or those with chronic or silent cardiovascular disease, who are additionally negatively affected by the circulatory stress associated with diving. Certainly the DAN data supports this possibility, but it is not known if DAN membership holders are representative of the wider diving population or how they might differ from other diving groups such as commercial divers. Likewise, we cannot say whether divers are a self-selected group to which people with pre-existing medical conditions are less likely to belong. Finally, it is not yet known if the life expectancy of lifelong divers is different from that of a comparable non-diving population.

Conclusion

Diving and aging independently affect the vascular endothelium and their combined effects need to be better understood. As the function of the vascular endothelium deteriorates with age, the resulting outcome for divers' health depends on a complex interaction between harmful and beneficial factors. Diving may further aggravate an already vulnerable situation, consistent with the elevated risk for male divers of dying in the water from a cardiovascular event. Alternatively diving may provide protection through processes of acclimatization, as suggested by the lower relative risk of decompression sickness in older, experienced divers and the lasting changes in blood biochemistry after extensive diving. Since endothelial biochemistry is comparable between man and rodent, such animal studies may aid in the elucidation of the combined effects of diving and aging on the cardiovascular health of aging divers.

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Acknowledgements

This work was supported by grants from the Norwegian Research Council under Petromaks project no. 20546, Statoil ASA and the Partenariat Hubert Curien (PHC) Aurora programme for French Norwegian researcher exchange to promote new project collaborations. Peter Buzzacott received funding for the preparation of this manuscript from the People Programme (Marie Curie Actions) of the European Union's Seventh Framework Programme FRP/2007-2013/ under REA grant agreement no. 264816.

Conflict of interest: nil

Submitted: 12 October 2014; revised 15 April, 11 August and 12 November 2015
Accepted: 13 November 2015

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Short communications

Cerebrospinal fluid markers of central nervous system injury in decompression illness – a case-controlled pilot study

Pashtun Shahim, Per Arnell, Andreas Kvarnström, Anders Rosén, Daniel Bremell, Lars Hagberg, Kaj Blennow and Henrik Zetterberg

Abstract

(Shahim P, Arnell P, Kvarnström A, Rosén A, Bremell D, Hagberg L, Blennow K, Zetterberg H. Cerebrospinal fluid markers of central nervous system injury in decompression illness – a case-controlled pilot study. *Diving and Hyperbaric Medicine*. 2015 December;45(4):240-243.)

Introduction: Decompression sickness (DCS) may cause a wide variety of symptoms, including central nervous system (CNS) manifestations. The main objective of this study was to examine whether DCS is associated with neuronal injury, and whether DCS could result in altered amyloid metabolism.

Methods: Seven, male divers with DCS and seven age-matched controls were included in the study. All the divers were treated by recompression but the controls did not receive hyperbaric oxygen. Cerebrospinal fluid (CSF) samples were collected 7–10 days after the diving injury and at three months follow-up. CSF biomarkers of neuronal injury, astroglial injury/activation, and a range of markers of amyloid β (Aβ) metabolism, as well as two proinflammatory interleukins, were analysed using immunochemical methods.

Results: There were no significant differences in the best-established CSF markers of neuronal injury, total tau (T-tau) and neurofilament light, between DCS patients and controls or between the two sampling time points. Also, there were no significant changes in the astroglial or amyloid (Aβ)-related markers between DCS patients and controls. However, the only diver with CNS symptoms had the highest levels of CSF T-tau, Aβ38, Aβ40 and Aβ42.

Conclusion: The results of our study speak against subclinical CNS injury or induction of inflammation or amyloid build-up in the brain among the six DCS patients without neurological symptoms. Further research, including on divers with CNS DCS, is justified.

Key words

Decompression sickness; central nervous system; injuries; inflammation; biomarkers

Introduction

Decompression sickness (DCS) is considered to be caused both by in situ bubble formation from dissolved inert gas, and arterial gas embolism, in which alveolar gas or venous gas emboli enter the arterial circulation via intra-cardiac or pulmonary right-to-left shunts. Manifestations can range from musculoskeletal and skin symptoms, to neurological symptoms and death. The standard treatment is recompression in a hyperbaric chamber following well-established protocols.[1]

Studies suggest that persistent foramen ovale (PFO) increases the risk of neurological symptoms and also asymptomatic ischaemic episodes in DCS by providing a means for arterial gas bubbles to directly reach the brain.[2]

Data are accumulating which indicate that brain hypoxia plays a role in the pathogenesis of Alzheimer's disease.[3] One of the hallmarks of Alzheimer's is the accumulation of amyloid β (Aβ) plaques.[4] In animal models of Alzheimer's, transient hypoperfusion results in an acute increase in Aβ by induction of the β-secretase metabolic pathway of amyloid precursor protein (APP), with formation of diffuse Aβ plaques.[5] In humans, increased Aβ expression has been reported in pyramidal neurons of the hippocampus in response to cerebral ischaemia.[6] A variety of biochemical markers have been used to investigate Alzheimer's.[7]

The main objective of this study was to examine in a group of divers presenting with DCS whether there were biochemical signs of brain injury, including in the absence of overt neurological symptoms. Further, we examined whether DCS could result in altered Aβ metabolism and neuroinflamation.

Material and methods

Seven male divers (average age 32, range 24–44 years) were recruited from June 2009 to May 2013 upon admission for hyperbaric oxygen treatment for DCS. All seven received a US Navy Treatment Table 6. The study was approved by the Ethics Committee for Medical Research at the University of Gothenburg. Written informed consent was obtained from all participants. Cerebrospinal fluid (CSF) was collected by experienced anaesthesiologists using 20-g Sprotte needles 7–10 days after the decompression incident.[8] This is the optimal time to detect neurological injury in acute conditions such as stroke[9] and traumatic brain injury.[10] A second sample

Table 1
Cerebrospinal fluid biomarkers measured in this case-controlled study of divers with decompression sickness

Total tau	T-tau
Neurofilament light	NFL
Visinin-like protein	VILIP-1
Glial fibrillary acidic protein	GFAP
mammalian chitinase-like protein	YKL-40
Amyloid β	Aβ38; Aβ40; Aβ42
Amyloid precursor proteins	sAPP-α; sAPP-α
Interleukins	IL-6; IL-8

was taken at three months follow-up, by which time any biomarker abnormality should have normalized.[9]

Of the seven patients, six had peripheral DCS symptoms and one patient had central nervous system (CNS) symptoms. Two patients had a PFO on transoesophageal echocardiography (TEE), while the rest had normal TEE. For comparison, seven age- and sex-matched controls were included from a previously described group of neurologically healthy volunteers, collected at the same hospital using identical sampling and sample handling protocols.[11]

BIOCHEMICAL PROCEDURES

All CSF samples were collected by lumbar puncture in the L3/L4 or L4/L5 interspace, centrifuged at 2,000 g at 4^{O}C for 10 min, aliquoted and stored at −80^{O}C pending batch analysis. Three sensitive CSF markers of neuronal injury (total tau, T-tau; neurofilament light, NFL;[12,13] visinin-like protein 1, VILIP-1[12]), two markers of astroglial injury/activation (glial fibrillary acidic protein, GFAP; YKL-40[12]), and a range of markers of amyloid β (Aβ) metabolism,[14] as well as two proinflammatory interleukins (IL-6 and IL-8)[15] were assayed using standard immunochemical methods (Table 1).

STATISTICAL ANALYSIS

For the paired observations, the Wilcoxon signed rank test was used. For the group comparison of the biomarkers versus controls, the Mann-Whitney *U* test was used. All tests were two-sided and statistical significance was determined at $P < 0.05$. For multiple group comparison, the Kruskal-Wallis test with post-hoc Dunn's test was used. All statistical analyses were performed using GraphPad Prism 5.0 (GraphPad Inc., San Diego, CA).

Results

CLINICAL DATA

Of the seven divers, six had upper limb (mainly shoulder) joint pains and one presented with join pains, vertigo and paraesthesiae. Delay to recompression treatment varied from nine to 57 hours, though all but one diver presented within 24 h. Two divers, including the one with central nervous system (CNS) symptoms, had a PFO, identified by transoesophageal echocardiography (TEE), while the other five had a normal TEE. None of the participants reported post-lumbar puncture headache.

BIOMARKERS OF NEURONAL AND ASTROGLIAL INJURY

There were no statistically significant differences in CSF concentrations of T-tau, NFL and VILIP-1 between the two groups or over time (Table 2). There were also no significant differences in the level of CSF GFAP and YKL-40 compared to controls or over time (Table 2).

The diver with a PFO and CNS symptoms had the highest levels of T-tau at admission and at the three-month follow-up (632 pg·ml^{-1} and 726 pg·ml^{-1} respectively), whereas the diver with a PFO but no CNS symptoms had normal biomarker levels.

BIOMARKERS OF AMYLOID PATHOLOGY

There were no statistically significant differences in CSF concentrations of Aβ metabolism between the two groups or over time (Table 2). The diver with CNS symptoms had the highest CSF levels at admission and at the three-month follow-up of Aβ38 (3,330 pg·ml^{-1} and 3,625 pg·ml^{-1} respectively), Aβ40 (19,235 pg·ml^{-1} and 21,547 pg·ml^{-1} respectively) and Aβ42 (2,190 pg·ml^{-1} and 2,414 pg·ml^{-1} respectively).

INFLAMMATORY BIOMARKERS

There were no significant differences in the levels of CSF IL-6 in DCS patients compared to controls (Table 2). However, the levels of CSF IL-8 were lower in DCS patients during admission and at follow-up as well as compared to controls, but these decreases were not statistically significant (Table 2). There were also no differences in either CSF IL-6 or IL-8 levels over time. There were no correlations between the levels of any of the biomarkers and the time to recompression therapy (data not shown).

Discussion

Biomarkers of neurological injury in divers with DCS have not been reported previously. We were interested to see whether DCS affects Alzheimer's-related amyloid metabolism or alters biomarkers for neuraxonal damage, astroglial injury, and inflammation. The main finding from this pilot study was that there were no differences in well-established CSF markers of neuronal injury, T-tau and NFL, between divers with DCS and controls or over time post injury and recompression treatment. These markers are

Table 2
Cerebrospinal fluid biomarkers (means, 95% confidence intervals) in seven divers with decompression sickness and seven age-matched controls; there were no significant differences between the initial and 3-month values or at either time between the divers and the control group (see Table 1 for details of biomarkers)

Biomarker (pg·mL^{-1})	**7–10 days after DCS**		**3-month follow-up**		**Control group**	
T-tau	321	175–466	377	99–554	270	212–327
NFL	334	235–434	1,270	1,009–3,550	360	266–454
VILIP-1	203	12–394	232	49–415	72	34–110
GFAP	247	136–357	246	136–356	245	44–447
YKL-40	58,682	44,730–72,635	74,169	46,063–102,275	74,022	49,965–98,079
Aβ38	1,915	1,291–2,539	2,014	1,228–2,799	1,903	1,527–2,278
Aβ40	12,771	8,549–16,993	13,753	8,629–18,123	13,753	11,349–16,158
Aβ42	1,412	961–1,863	1,354	869–1,839	1,473	1,249–1,697
sAPP-α	962	769–1,156	1,016	808–1,224	988	694–1,282
sAPP-β	679	459–899	670	423–976	613	429–798
IL-6	1.2	0.84–1.54	1.1	0.80–1.34	1.2	0.78–1.6
IL-8	45	35–56	44	32–56	55	44–67

highly sensitive and specific for CNS injury and can also identify sub-concussive neuroaxonal injury following mild head trauma.[16,9]

Compared to controls, the divers had slightly elevated CSF levels of VILIP-1 at both time points. However, the lack of dynamic change in this marker speaks against the elevation being related to DCS, and it was not statistically significant.

Nor were we able to address whether PFO per se is a risk factor for aberrant CSF biomarkers for neuronal injury and Aβ metabolism. In the one study on the association of PFO with Alzheimer's disease and vascular dementia, the odds ratios did not differ significantly.[17]

One plausible reason for the reduced levels of IL-8 in the divers might be the fact that the pro-inflammatory cytokines were measured at seven days post recompression, whereas previous studies have shown that the levels of pro-inflammatory cytokines may peak at earlier time-points. Further, hyperbaric oxygen therapy may also modify the levels of pro-inflammatory cytokines.[18,19]

Seven days after the diving accident was chosen for sampling as this is optimal for neuronal injury and Aβ markers, but perhaps not for cytokines. CSF sampling at an earlier time point was not considered for ethical reasons as it is unclear if CSF sampling closer to a diving accident could influence cerebrovascular bubble formation.

The main limitation of this study is the small sample size. Nevertheless, the results speak against subclinical CNS injury or induction of inflammation or amyloid build-up in the brain of divers without symptoms and signs of CNS injury. With only one diver presenting with neurological symptoms, no conclusions can be drawn with regard to more serious injuries. We believe that these findings warrant further investigation in a larger cohort of divers, including those with CNS DCS.

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Acknowledgements

We thank David Pazooki, all study participants and the recompression chamber staff.

Funding

The study was supported by grants from the Swedish Research Council, Swedish State Support for Clinical Research (LUA-ALF), the Alzheimer Foundation, the Knut and Alice Wallenberg Foundation and the Torsten Söderberg Foundation.

Conflict of interest

The authors report no conflicts of interest. KB has served on Advisory Boards for Eli-Lilly, IBL International and Roche Diagnostics.

Submitted: 24 February 2015; revised 09 July and 15 October 2015
Accepted: 19 October 2015

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Comparison of Australian and New Zealand referral rates for hyperbaric oxygen in oro-facial osteoradionecrosis: evidence-based, funding constraint or clinician whim?

Christopher Sames, Desmond F Gorman, Peter Sandiford and Lifeng Zhou

Abstract

(Sames C, Gorman DF, Sandiford P, Zhou L. Comparison of Australian and New Zealand referral rates for hyperbaric oxygen in oro-facial osteoradionecrosis: evidence-based, funding constraint or clinician whim? *Diving and Hyperbaric Medicine*. 2015 December;45(4):244-246.)

Aim: To compare Australian and New Zealand (NZ) rates of referral to hyperbaric units for patients with, or at risk of developing mandibular or maxillary osteoradionecrosis (ORN) due to a history of radiotherapy for oro-pharyngeal cancer.

Method: Relevant patient treatment data from all hyperbaric units in Australia and NZ were collated and analysed.

Results: The rate of referral to hyperbaric units in Australia for treatment or prophylaxis of patients with, or at risk of oro-facial ORN, was 1.7 times the rate of referral in NZ. Within Australia, there was a greater than three-fold interstate variation.

Conclusion: There is a significant referral rate difference both within Australia and between Australia and NZ for hyperbaric oxygen therapy for oro-facial ORN. Possible reasons for this difference include access to funding, logistical difficulties, clinician preference for an alternative treatment and clinician attitudes to hyperbaric oxygen.

Key words

Hyperbaric oxygen therapy; osteoradionecrosis; evidence; survey

Introduction

There is good evidence that normal tissue is damaged by radiotherapy, and that bone, especially the mandible, is vulnerable to the development of osteoradionecrosis (ORN).[1] This has been described as a defect in wound healing and the risk is increased by trauma or surgical procedures.[2–4] Once established, the requirement for both surgical debridement and adjunctive hyperbaric oxygen (HBO) is uncertain. Some of the uncertainty is likely attributable to a single randomised controlled trial (RCT) that showed that, in moderate cases, HBO alone conferred no benefit over surgery alone.[5] However, this study assessed HBO as a primary rather than adjunctive treatment; by contrast, the generally advocated, multidisciplinary Marx protocol is a combination of HBO and thorough debridement of necrotic bone.[6] In this context it is accepted that HBO does not obviate the need for complete surgical debridement.[7]

In a systematic review of the use of HBO for delayed radiation injuries, 14 published studies are cited, which review the application of HBO to ORN of the mandible.[8] Of these, one was a small RCT (12 patients) and the others were case series. All but one showed an advantage using HBO in treating existing ORN of various stages. In the study that did not show an advantage, HBO was only given post-operatively, thus supporting Marx's general principle that HBO is important prior to surgical wounding in irradiated tissues.[9] In view of reported high success rates in advanced cases of ORN using microvascular reconstruction without HBO, the weight of evidence may be moving in favour of limiting the use of HBO to moderate and mild cases.[10]

The reported incidence of ORN has varied over the decades since Marx's original study, probably due to improved surgical and radiotherapy techniques such as intensity modulated radiotherapy (IMRT). Two controlled studies comparing ORN incidence post dental extraction reported rates of 5% vs. 30% and 3% vs. 14% with or without prophylactic HBO respectively.[4,11] Several studies have shown that risk increases with radiation dosage, time since radiation, trauma (such as dental extraction) and poor oral hygiene. Spontaneous development of ORN occurs in 5–15% with older technologies, and is as low as 0–6% using newer technologies.[12–15] These lower rates have called into question the ongoing need for HBO, but they do not take account of the additional impact of dental extraction, and there are no published relevant controlled trials. Comprehensive systematic reviews have concluded that the evidence is limited and conflicting, and although HBO shows promise, better quality studies are needed.[16,17]

The practice of performing a tooth extraction or other surgery in an irradiated field without prescribing HBO is not uncommon. A UK survey showed that a third of dental and maxillofacial clinicians never prescribe HBO, and in a more recent US study comparing the attitudes of radiation oncologists and hyperbaric physicians, of the 37% of radiation oncologists and 18% of hyperbaric physicians who do not recommend HBO for prophylaxis of ORN, 52% and 38% respectively cited 'lack of evidence' as the reason.[18] Not surprisingly, a majority of both groups supported further RCTs.[19] In Denmark, most of the relevant referring clinicians considered HBO helpful in ORN but felt that the existing level of evidence was a barrier to referral.[20]

An informal review of cases referred to a New Zealand (NZ) hyperbaric unit identified a significant number of patients in whom surgery or tooth extraction was undertaken in an irradiated field without referral for prophylactic HBO. Clearly, it is possible that irradiated patients who are at risk of developing mandibular or maxillary ORN, and who might benefit from HBO as an adjunct to any dental or maxillofacial surgical procedure, may not receive such care.

The aim of this study was to determine whether there is a difference between the rates of referral in NZ and Australia, and also between the Australian states. A significant difference may imply inappropriate under or over-treatment, or preference for an alternative treatment for ORN.

Method

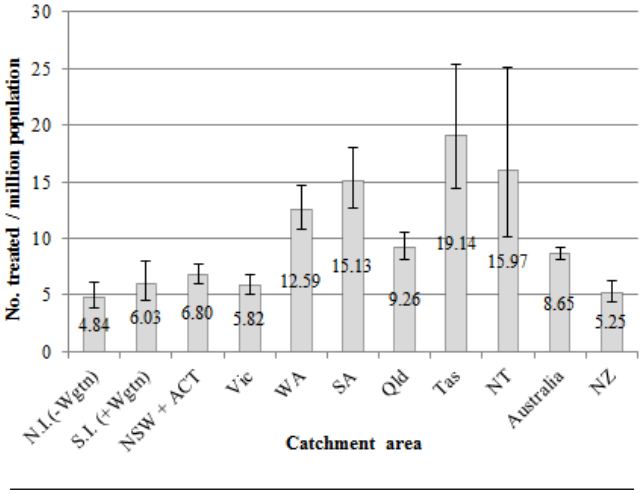
This study was approved by the Waitemata District Health Board Human Ethics Committee (reference number RM13034). Data collected from all Australian and NZ hyperbaric units by the Hyperbaric Technicians and Nurses Association between 01 July 2009 and 30 June 2014 were reviewed, and the figures relating specifically to mandibular or maxillary ORN were collated and analysed. Population estimates published on the websites of the Australian Bureau of Statistics and Statistics New Zealand were used to derive referral numbers per million of population from the relevant catchment areas. Because the raw data set was anonymised, comprising only the numbers of patients treated at the units, analysis of patient demographics was not possible.

The accuracy of the comparisons between Australia and NZ are based on the assumption that the age/sex distribution of the Australian and NZ populations is similar. Comparison between Australian states also depends on the assumption that patients accessed HBO in their own catchment area, apart from those in the Australian Capital Territory (ACT) who accessed HBO at New South Wales (NSW) units. The 95% confidence limits were calculated assuming a Poisson distribution of HBO intervention counts and error-free population estimates. The significance of the variations in referral rates between Australian states and between Australia and NZ was tested using the Poisson regression model. Statistical analysis was undertaken using SAS9.4.

Results

The mean rate of referral to hyperbaric units in Australia for treatment or prophylaxis of patients with, or at risk of oro-facial ORN was significantly higher than the rate in New Zealand (rate ratio 1.7, 95% confidence limits (CI): 1.4, 2.0). There was also significant variation in referral rates between Australian states, with Victoria having a significantly lower rate, and Tasmania a significantly higher rate than the rest of Australia. Figure 1 shows the area-specific mean HBO referral rates with 95% CIs. In New Zealand, patients resident in the Wellington (Wtgn) catchment area (in the south of the North Island) are referred to the Christchurch hyperbaric unit (in the South Island) for proximity reasons, hence the categories N.I.(-Wgtn) and S.I.(+Wgtn) in Figure 1.

Figure 1
Mean numbers of patients with osteoradionecrosis of the jaw treated with hyperbaric oxygen per million population 01 July 2009–30 June 2014 for each Australian state and the two regions of New Zealand; bars represent 95% confidence intervals



Discussion

Lack of a specific ICD-10 code for oro-facial ORN made it impossible to estimate hospital-based incidence or treatment rates in either Australia or New Zealand, but it seems unlikely that these would vary sufficiently to account for such significantly different referral rates on purely clinical grounds. The impact of logistical issues such as travel, accommodation and the significant time commitment cannot be ignored, and it is likely that some patients will decline treatment if they have to be away from home for six weeks. Clinician preference for the recently introduced treatment of ORN with a combination of pentoxifylline, vitamin E and clodronate (Pentoclo) over 1–2 years in some regions, but not others, could contribute to regional variation. An audit of treatment preference among the relevant clinicians would help clarify this matter.

Other possible reasons for variation in referral rates are; mode of radiation delivery (IMRT being the most likely, but not invariable, and data not available for this study), access to funding, and clinician attitudes to the use of HBO for ORN. In Australia, funding for HBO in oro-facial ORN is readily available from three sources in all states, namely; state health departments, Medicare and private health insurance. Thus, the three-fold interstate referral variation is more likely due to clinician experience with, or attitude to, HBO use for ORN. There is no reason to believe that the attitudes of Australian or NZ clinicians are likely to differ from those in the UK, USA or Denmark, previously mentioned.[18–20]

In NZ, the only funding source until very recently has been via individual District Health Boards, and this has certainly been an impediment to HBO access for some patients. The

lower referral rate in NZ cannot, therefore, be attributed solely to clinician attitude. With the recent adoption of HBO funding in NZ by the National Health Board, funding barriers to referral have been removed, so more accurate comparisons with Australian referral rates are likely in the future.

We accept that a limitation of this audit is due to the difficulty in collecting accurate data from all of the hyperbaric units. In this regard, it was unfortunate that a number of small, privately operated hyperbaric units in New South Wales and Victoria declined to participate in this study. Higher referral numbers in NSW and Victoria would reduce the inter-state variations in Australia, but they would increase the variation between Australia and NZ. We also accept that the above data refer to 'treatment' rates, but we have chosen to use this as a surrogate for 'referral' rates, on the basis that referral for ORN is exceedingly unlikely to result in refusal to treat.

If clinician attitude is the reason for the apparent under-use of HBO in oro-facial ORN, this is understandable on the basis of conflicting reports and paucity of high-grade evidence. Moreover, verification of HBO efficacy in ORN treatment requires further high-quality research, and this will in turn depend on improvements in the ICD coding system so that patients can be identified from clinical databases.

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Conflict of interest: nil

Submitted: 10 April 2015; revised 02 October 2015
Accepted: 15 October 2015

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Technical report

A CT-, PET- and MR-imaging-compatible hyperbaric pressure chamber for baromedical research

Kasper Hansen, Esben SS Hansen, Lars P Tolbod, Martin C Kristensen, Steffen Ringgaard, Alf O Brubakk and Michael Pedersen

Abstract

(Hansen K, Hansen ESS, Tolbod LP, Kristensen MC, Ringgaard S, Brubakk AO, Pedersen M. A CT-, PET- and MR-imaging-compatible hyperbaric pressure chamber for baromedical research. *Diving and Hyperbaric Medicine*. 2015 December;45(4):247-254.)

Objectives: We describe the development of a novel preclinical rodent-sized pressure chamber system compatible with computed tomography (CT), positron emission tomography (PET) and magnetic resonance imaging (MRI) that allows continuous uncompromised and minimally invasive data acquisition throughout hyperbaric exposures. The effect of various pressures on the acquired image intensity obtained with different CT, PET and MRI phantoms are characterised.

Material and methods: Tissue-representative phantom models were examined with CT, PET or MRI at normobaric pressure and hyperbaric pressures up to 1.013 mPa. The relationships between the acquired image signals and pressure were evaluated by linear regression analysis for each phantom.

Results: CT and PET showed no effect of pressure per se, except for CT of air, demonstrating an increase in Hounsfield units in proportion to the pressure. For MRI, pressurisation induced no effect on the longitudinal relaxation rate (R_1), whereas the transverse relaxation rate (R_2) changed slightly. The R_2 data further revealed an association between pressure and the concentration of the paramagnetic nuclei gadolinium, the contrast agent used to mimic different tissues in the MRI phantoms.

Conclusion: This study demonstrates a pressure chamber system compatible with CT, PET and MRI. We found that no correction in image intensity was required with pressurisation up to 1.013 mPa for any imaging modality. CT, PET or MRI can be used to obtain anatomical and physiological information from pressurised model animals in this chamber.

Key words

Pressure chambers; radiological imaging; pressure; animal model; equipment; hyperbaric research

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Introduction

Computed tomography (CT), positron emission tomography (PET) and magnetic resonance imaging (MRI) are routinely used to visualise internal morphology and quantify basic physiological parameters non-invasively. While CT visualises particularly hard tissues, MRI can visualise soft tissue anatomy and is capable of measuring certain physiological parameters and metabolites. PET uses synthesized, radiolabelled tracers, which mimic endogenous bioactive species, to examine specific metabolic processes. Combination of such imaging systems and pressure chambers has the potential to non-invasively investigate fundamental structural, physiological and metabolic processes in the acute phases of compression and decompression: stages in experimental barometric research studies which have traditionally been very challenging due to the limited accessibility to the model animal inside the pressure chamber.

Specialised chambers have been constructed for preclinical and animal research,[1,2] but these systems unfortunately are incompatible with most medical imaging systems. Recently a commercial manufacturer has introduced a preclinical MRI-compatible pressure chamber, available up to a relatively low pressure.[3] We describe a simple, cost-effective, imaging-compatible pressure chamber system that facilitates simultaneous CT, PET and/or MRI of rodents over a range of pressures from 101.3 kPa to 1.013 mPa (equivalent to 90 metres' sea water (msw)).

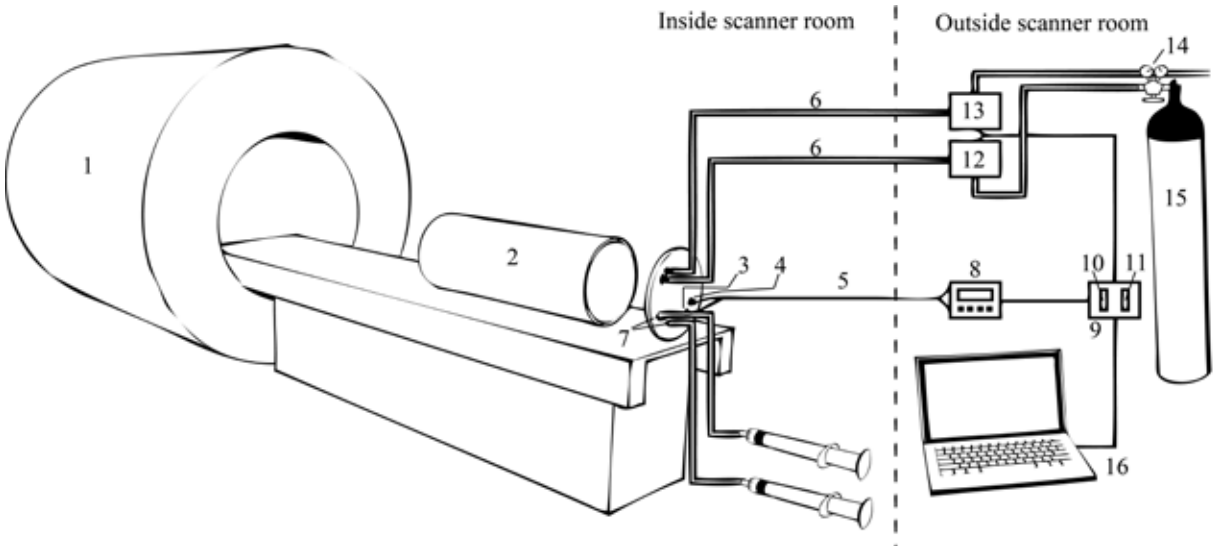
Materials and methods

CONSIDERATIONS

Materials used for pressure chamber systems should comply with basic CT, PET and MRI physics requirements. In short, because CT uses characteristic X-ray attenuation to create shadow images of the traversing radiation (photons), the materials used should neither block nor scatter the X-ray radiation. Similarly for PET, the characteristic 511 keV photons emitted from the site of positron annihilation should traverse the chamber material readily. On the other hand, MRI systems use extremely strong magnetic fields together with powerful radiofrequency pulses to produce an image that is dependent on the distribution of hydrogen in the body, so the material must be completely non-magnetic, non-electrically conductive, and not disturb the emitted radio frequencies.

Figure 1

System overview; 1 – imaging system (CT, PET or MRI); 2 – imaging compatible pressure chamber; 3 and 4 – pressure and temperature sensors (optical technology); 5 – optical fibre extension cables (10 m long); 6 – flexible high-pressure polyamide pneumatic tubing (Ø/ø: 4/6 mm, 10 m long) connected to pressure chamber and pressure control unit through acetal-based snap-in pneumatic plugs; 7 – Pressure-tight cable and catheter penetrations; 8 – optical to digital signal converter; 9 – A/D converter; 10 – sensor output interface; 11 – interface for solenoid valve control; 12 – proportional solenoid valve for gas-inlet; 13 – plunger valve for gas-output control; 14 – pressure reducing valve (displaying safety redundancy; hence, the inlet pressure is reduced well below the pressure limits of the system components); 15 – compressed gas cylinder (allows the use of any premixed gas mixture); 16 – computer system (for pressure profile execution and data acquisition through various third-party software providers). Full details of the specific equipment used is available from the authors.



DESIGN

Figure 1 shows a schematic drawing of the pressure chamber system. The non-magnetic pressure chamber is positioned inside the scanner and connected to an automated pressure control device that, for use in MRI, must be located outside the scanner room. PVC rods, PVC union flanges and acetal-based snap-in pneumatic plugs used for the system were purchased CE-certified for working pressures up to 1.621 mPa. A PVC-union flange was mounted to each end of the 400 mm long PVC-rod (internal/external diameter: 100/110 mm) using PVC glue. Transparent polycarbonate plate (thickness 15 mm) was cut to precisely fit the recess inside a threaded union-flange-cap, thereby aiding as end plates compressing the axially positioned O-ring seals in the union-flanges. Before use, the system was safety tested through multiple pressurisations to double the intended working pressure (to 2.026 MPa). Additional component details are included in the Figure 1 legend.

PRESSURISATION AND INSTRUMENTATION

Compressed atmospheric gas (air) was delivered through flexible polyamide hoses, connected to the control unit and pressure chamber through snap-in pneumatic plugs. Two hoses were fitted to the pressure chamber, one in either end to ensure efficient gas exchange and to avoid excessive carbon dioxide (CO_2) build up during an animal experiment. Accordingly, chalk scrubbers inside the pressure chamber could be used to remove CO_2 further in animal experiments. Pressure-tight penetrations allowed insertion of fibr optic pressure and temperature probes. Further, PE-hoses were used to construct a circulating water-loop, allowing temperature feedback regulation (this option was not used during phantom scans). The pressure and temperature inside the chamber may be controlled remotely from the scanner's control room. An automated pressure-control unit was built to ensure reproducible pressure profiles while scanning, using LabVIEW 2013 software (National Instruments).

SCANNING PROCEDURES AND PHANTOMS

The effect of hyperbaric conditions on the acquired CT, PET and MRI images were investigated using phantom models. Individual phantoms were scanned multiple times including initial scans at normobaric pressure (101.3 kPa) outside the pressure chamber, followed by normobaric scans inside the pressure chamber. Additional scans were performed at pressures of 203, 405, 608, 810 kPa, 1.013 mPa, and a final scan after a short decompression period.

CT

The phantoms were homogeneous cylindrical material rods (length 5 cm, diameter 2 cm) of acrylic, polypropylene, polyethylene, teflon or bone, immersed in sterile water. Two vials containing demineralised water and air inside the pressure chamber were also used as phantoms.

PET

Two vials (PET phantom A, PET phantom B) containing 35 mL demineralised water with initial radioactive gamma-activities of 40 and 80 kBq·mL^{-1} respectively provided by addition of the PET tracer ^{18}Fluorodeoxyglucose.

MRI

A gadolinium (Gd)-containing contrast agent (279.3 mg Gd·mL^{-1}, Dotarem) was dissolved in demineralised water in concentrations of 0, 0.5, 1.0 and 2.0 mM, and the solutions were degassed by heating to 80^{O}C in an ultrasound device for 120 min. This process provoked nucleation of dissolved gas, which could be removed by applying vacuum using gastight syringes pulled hard to provoke further nucleation after cooling to room temperature. Any visible gas inside the syringes was carefully removed. MRI phantoms were kept in filled, airtight vials to avoid gas exchange with the surroundings. The MRI phantoms were kept at room temperature (21^{O}C) during the study period.

IMAGING SYSTEMS AND ACQUISITION PROTOCOL

CT

GE Medical Systems (Discovery 690®). Rotation time: 0.5 s, energy level 120 kV, tube current: 200 mA, slice thickness: 1.25 mm, slice spacing: 0.63 mm, feed/rotation: 39.38 mm.

PET

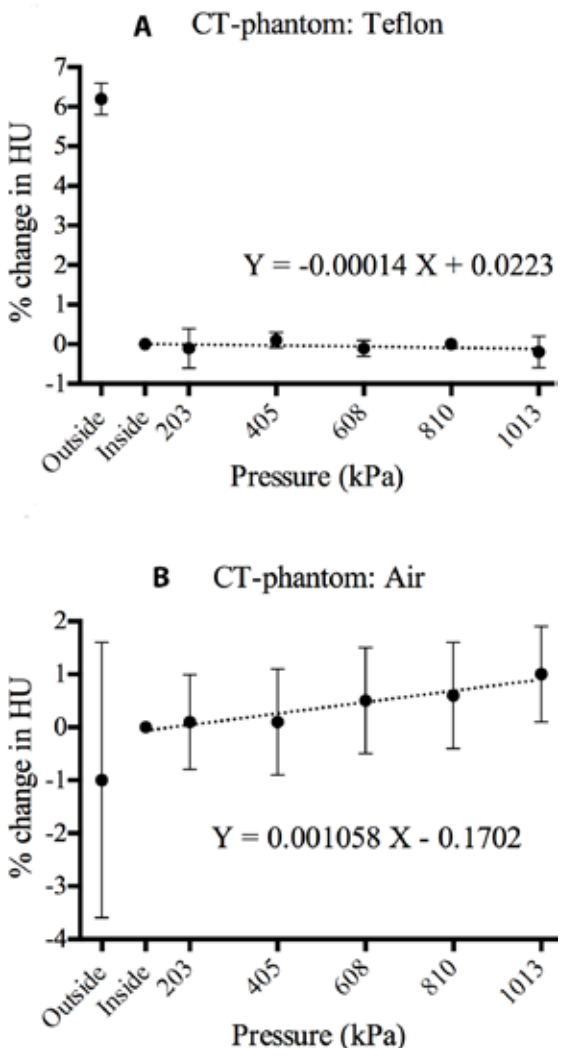
GE Medical Systems (Discovery 690®). Scanning time: 3 min, number of slices: 47, image matrix size: 1.82 × 1.82 × 3.27 mm^3. Images were reconstructed using the VuePoint HD SharpIR algorithm (3 iterations, 24 subsets, 4 mm 2D Gaussian post filter in the transaxial plane and a 3-point convolution axial filter ('light' filter [1, 6, 1]/8)) with standard CT attenuation and scatter correction.

MRI:

T Siemens MRI system (Magnetom Skyra®). The pressure chamber fitted exactly into a 32-channel transmit/receive knee radiofrequency coil. For R_1 measurements, a Look-Locker approach (inversion-recovery True-FISP sequence) with 288 inversion-times was used, whereas a spin-echo sequence with 16 echo times (TE) (40–640 ms) was used for R_2 measurements. R_1 protocol: scanning time: 3:23 min, resolution matrix: 80 × 44, FOV: 153 × 84 mm^2, slice thickness: 7 mm, repetition time: 3.12 ms, TE: 1.35 msec, flip angle: 5°. R_2 protocol: scanning time: 2:50 min, resolution matrix: 64 × 41, FOV: 75 × 75 mm^2, slice thickness: 7.0 mm, repetition time: 4000 ms, TE: 40–640 ms.

Figure 2

Representative results from CT scans of phantoms, teflon (A), and air (B), respectively; scans were performed at normobaric pressure both outside and inside the pressure chamber 101.3 kPa and at various pressures between 203 kPa and 1.013 MPa; values are the relative % differences from normobaric values inside the pressure chamber (mean ± SD), *n*-values as in Table 1. The slope of the regression for Teflon phantom was not significantly different from zero, whereas the slope of the air regression (B) was (N.B. these slopes are calculated from the percentage change of HU with pressure, whereas slopes reported in Table 1 are calculated directly from HU- values).



DATA ANALYSIS AND STATISTICS

Image analyses were performed with the OsiriX software (version 5.5.1, 64-bit). Statistical analyses were performed in STATA 12.0 and PRISM 6. Linear regression analysis was used to test the null hypothesis that pressure per se had no significant effect on the image signal. CT and MRI analyses were performed on raw data, while PET data were normalised before analysis because the data were obtained over three individual acquisitions, which resulted in slightly

Figure 3

PET scans of two ^{18}Fluorodeoxyglucose-based solutions with initial activities of 40 (A) and 80 kBq·mL^{-1} and (B), respectively; scans were performed at normobaric pressure both outside and inside the chamber. Values are relative % differences from normobaric values inside the chamber (mean ± SD); *n*-values as reported in Table 2; the slopes of the regressions were not significantly different from zero.

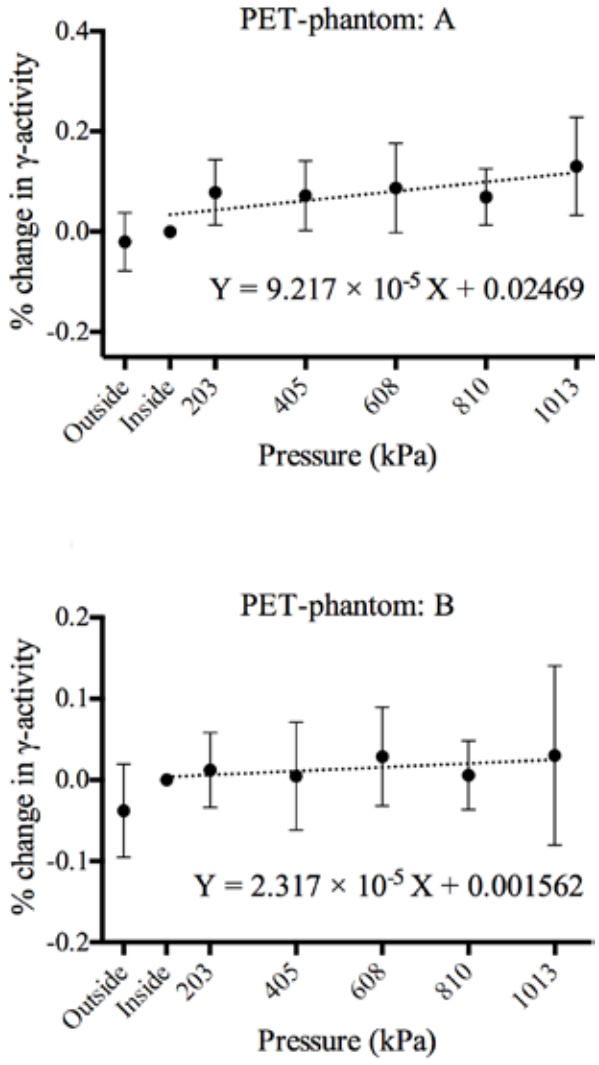
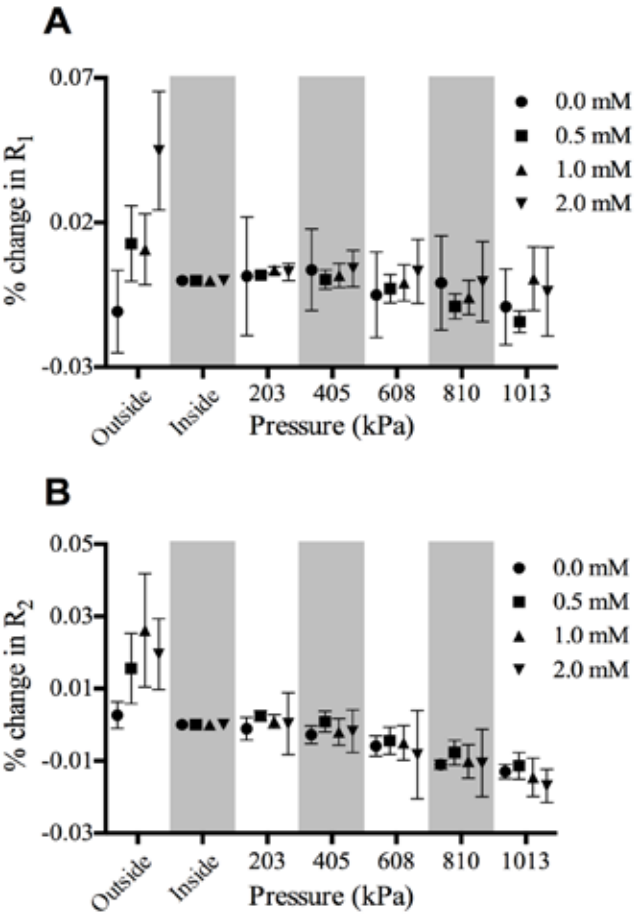


Figure 4

MRI scans using (A) T_1- and (B) T_2-weighted sequences of four degassed Gd-based phantoms ($R_1 = T_1^{-1}$, $R_2 = T_2^{-1}$); scans were performed at normobaria both outside and inside the chamber. Values are relative % differences from normobaric values obtained of phantoms inside the chamber (mean ± SD); all four phantoms were scanned at equal pressure(s) (white and grey areas indicate constant pressure equivalent to tick markings below) but data points have been nudged to avoid superimposed points; refer to Table 3 for regression coefficients and *n*-values.



different individual phantom-activities. The PET signal was corrected for radioactive decay.

A linear regression analysis was used to test whether the slope (the derivative of image intensity versus pressure) was significantly different from zero. Equation [1] describes the linear relationship for CT, Eq. [2] is for PET, and Eq. [3] is for MRI, assuming that different Gd-concentrations represent various magnetic relaxation properties of tissues:

$$HU_{(P)} = HU_{0(P=101\ kPa,\ \ Phantom\ material)} + \kappa' \times P \quad [1]$$

$$Activity_{(P)} = A_{0(P=101\ kPa)} + \kappa' \times P'' \quad [2]$$

$$R_{1,2\,(P,[Gd])} = R_{1,2\,(P=101\ kPa,\ [Gd]=0)} + r_{1,2(P)} \times P + r_{1,2([Gd])} \times [Gd] \quad [3]$$

where P is total pressure in units of kPa, and κ' and κ'' are specific material constants reflecting the material density to electromagnetic radiation for CT and PET, respectively. R_1 and R_2 are the longitudinal and transversal proton relaxation rates, $r_{1(P)}$ and $r_{2(P)}$ are longitudinal and transversal pressure-specific relaxivity constants, and $r_{1([Gd])}$ and $r_{2([Gd])}$ are the longitudinal and transversal Gd (paramagnetic)-specific relaxivity constants (where relaxivity denotes a change in relaxation per change in pressure or [Gd], respectively).

Results

We observed that pressure changes had no visible effects (e.g., noise or artefacts) on any phantom. The CT-measured HU for the teflon phantom was slightly reduced inside the pressure chamber compared to outside the chamber at normobaric conditions (Figure 2A). This is consistent with

Table 1
Linear regression analysis of CT phantoms scanned during pressurisation (101.3–1,013 kPa); intercept values are material-specific Hounsfield Units; the number of CT scans at each individual pressure were (kPa/*n*-value): 101(outside)/8, 101(inside)/4, 203/3, 405/3, 608/3, 811/3, and 1013/2.

CT phantoms	Regression (slope ± SEM)	Test values (slope)	Intercept (HU units ± SEM)	Test values (intercept)	R^2
Teflon	-0.0013 ± 0.0035	t = -0.38, P = 0.71	1390.07 ± 2.10	t = 661.53, P < 0.01	0.008
Bone	-0.0007 ± 0.0024	t = -0.30, P = 0.77	940.63 ± 1.43	t = 656.37, P < 0.01	0.005
Polypropylene	-0.0010 ± 0.0017	t = -0.59, P = 0.57	-98.10 ± 0.99	t = -98.68, P < 0.01	0.02
Acrylic	0.0005 ± 0.0021	t = 0.22, P = 0.83	123.39 ± 1.24	t = 99.90, P < 0.01	0.003
Polyethylene	0.0001 ± 0.0012	t = 0.08, P = 0.94	-85.33 ± 0.71	t = -119.77, P < 0.01	0.0004
Water	0.0008 ± 0.0013	t = 0.59, P = 0.56	-1.32 ± 0.79	t = -1.66, P = 0.107	0.012
Air	0.0107 ± 0.0008	t = 13.64, P < 0.01	-977.48 ± 0.46	t = -2126.35, P < 0.01	0.89

CT beam hardening caused by the PVC material used to construct the pressure chamber. The beam hardening artefact was, however, too small to have any measurable effect on the attenuation- and scatter-corrected PET images (Figures 3A and 3B). No magnetic inhomogeneity or RF disturbances were observed in the MRI data (Figures 4A and 4B).

The squared linear regression coefficient (R^2) varied greatly (range 0.001–0.99, Tables 1 and 2). We found very little effect of pressure on the signal obtained using the three imaging modalities. Representative graphs showing the acquired signal relative to the signal obtained inside the pressure chamber at normobaric pressure; CT (Figure 2A and 2B), PET (Figures 3A and 3B) and MRI (Figures 4A and 4B). The slopes of the linear regressions for the CT and PET data were not significantly different from zero, with the exception of the slope of CT scans of air, demonstrating a slope of 0.0107 ± 0.0008 HU × kPa^{-1}; significantly different from zero (t = -13.64, P < 0.01; Table 1). The slopes for CT phantoms in Table 1 were calculated directly from HU values, whereas the slopes in Figure 2 were calculated from the percentage change of HU with pressure and accordingly differ slightly from the values in Table 1. Linear regression analysis of PET phantoms scanned during pressurisation were not significantly different from zero.

For MRI, the longitudinal relaxivity (r_1) of Gd-phantoms of 0.0, 1.0, and 2.0 mM were not significantly affected by pressure, whereas the 0.5 mM phantom, in contrast, was significantly affected by -0.000037 ± 0.000015 s^{-1} × kPa^{-1} (mean ± SEM) (t = -2.98, P = 0.005; Table 3). The transversal relaxivity (r_2) of the Gd-phantoms were all slightly, but not significantly, affected by pressure (maximal effect was found for the 2.0 mM; -0.00019 ± 0.00006 s^{-1} × kPa^{-1} (mean ± SEM), t = -3.13, P = 0.004; Table 3). The MRI relaxivities were plotted against [Gd] (Figure 5), and

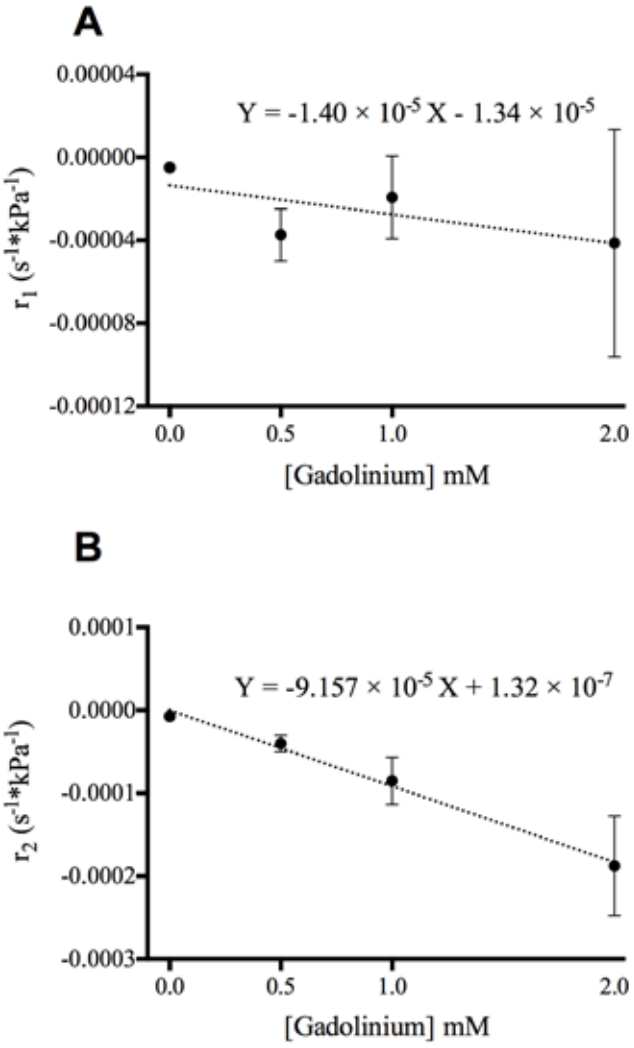
Table 2
Linear regression analysis of PET phantoms scanned during pressurisation were not significantly different from zero; scans at individual pressures were (kPa/*n*-value): 101(outside)/8, 101(inside)/4, 203/3, 405/3, 608/3, 811/3, and 1013/2.

PET phantom	Regression slope (± SEM)	Test values (slope)	R^2
A	0.00005 ± 0.00003	t = 1.47, P = 0.16	0.12
B	0.00003 ± 0.00002	t = 1.25, P = 0.23	0.09

Table 3
MRI of Gd-phantoms scanned during pressurisation (101–1,013 kPa); the pressure specific relaxivities (r_1 and r_2, s^{-1} × kPa^{-1}, respectively) were established through linear regression analysis of pressurised degased phantoms, i.e., the $r_{1,2}$ corresponds to changes in $R_{1,2}$ per change in kPa. The number of MRI-scans for all phantoms (in both r_1 and r_2) at each individual pressure were (kPa/*n*-value): 101(outside)/6, 101(inside)/6, 203/6, 405/6, 608/6, 811/6 and 1013/6.

MRI phantoms [Gd]		Relaxivity (±SEM)	Test values	R^2
r_1	0 mMol	-0.0000049 ± 0.0000024	t = -2.01, P = 0.052	0.11
	0.5 mM	-0.000037 ± 0.000015	t = -2.98, P = 0.005*	0.21
	1.0 mM	-0.0000192 ± 0.00002	t = -0.96, P = 0.343	0.03
	2.0 mM	-0.0000413 ± 0.000055	t = -0.75, P = 0.457	0.02
r_2	0 mM	-0.0000072 ± 0.0000011	t = -6.68, P < 0.001*	0.57
	0.5 mM	-0.00004 ± 0.0000098	t = -4.08, P < 0.001*	0.33
	1.0 mM	-0.000085 ± 0.000029	t = -2.98, P = 0.005*	0.21
	2.0 mM	-0.00019 ± 0.00006	t = -3.13, P = 0.004*	0.22

Figure 5
A possible interaction between pressure (kPa) and [Gd] was evaluated by plotting longitudinal (A) and transversal (B) pressure specific relaxivities (i.e., r_1 and r_2 values from Table 3) against [Gd]; the slope of r_2 was significantly different from zero, whereas the slope of r_1 was not.



linear regressions were performed to test for interactions between pressures per se and the concentration of gadolinium. There was no significant interaction between pressure and [Gd] for longitudinal relaxivity ($-1.40\times10^{-5} \pm 9.86\times10^{-6}$ $s^{-1} \times kPa^{-1} \times [Gd]^{-1}$ (mean ± SD), F = 2.01, P = 0.29, R^2 = 0.50), whereas a significant interaction on the transversal relaxivity resulted in a regression slope of $-9.157\times10^{-5} \pm 5.772\times10^{-6}$ $s^{-1} \times kPa^{-1} \times [Gd]^{-1}$ (mean ± SD), F = 251.7, P = 0.0039, R^2 = 0.99 (Figure 5).

Discussion

The aim of this study was to develop a CT-, PET- and MRI-compatible hyperbaric pressure chamber system and to quantify the effect of pressure per se over a range of pressures up to 1.013 MPa on the acquired signals in appropriate tissue-representative phantoms. We found that changes in pressure had no important influence on the image signals.

Recent studies using imaging-based systems in the investigation of diving-related symptoms of decompression sickness (DCS), have mainly included scans performed after pressure exposures, either acutely[4,5] or days, month or years after pressure exposure(s).[6–10] CT, PET and MRI could be used during the hyperbaric or hypobaric period if the pressure chamber materials comply strictly with the underlying physics of the scanner systems. Today, imaging compatible pressure chamber systems have only been used in a few studies; two studies of hyperbaric oxygen (maximum pressurisation to 405 kPa) and one for CT examination of lung compression in seal and dolphin cadavers (using a water-filled system pressurised up to 1.220 mPa).[11–13]

With CT, there is a beam-hardening effect resulting from absorption of low-energy X-rays in the pressure chamber material, with the effect that only the higher energies of the X-ray spectrum are traversing the pressure chamber and internal objects. Accordingly, these X-rays also penetrate the scanned object more easily, resulting in a small but evident HU-shift as demonstrated in Figure 2.[14,15] However, any contributing effects on the image signal induced by the pressure chamber itself are only problematic when comparing the signal acquired from objects outside the chamber with the acquired signal of the phantom inside the chamber. All data obtained from the CT phantoms (Table 1) were statistically unaffected by elevated pressure with the exception of air. The increase in X-ray density in the pressurised air corresponded to the linear increase in air density with pressure (Table 1).

Changes in pressure did not significantly affect the PET signal obtained from the two solutions of ^{18}Fluorodeoxyglucose (Table 2 and Figure 3) and no important artefacts were induced by the pressure chamber system.

For MRI, the use of degassed distilled water phantoms at 21°C revealed a non-significant effect of pressure with a slightly negative longitudinal relaxivity (Table 3, Figure 4A). Note, however, that the relaxation properties of water molecules depend on the applied magnetic field. In this study, we used a magnetic field strength of 3 Tesla, and the resulting T_1-relaxation ($1/T_1 = R_1$) of degassed phantoms at normobaric pressure was 1988 ± 7.3 ms (mean ± SEM; data not shown). Using a temperature correction of distilled water at 3 T of 0.106 s × $^{O}C^{-1}$ (SEM: 0.009 s × $^{O}C^{-1}$)[16], our measured relaxation rate of 0.27 s^{-1} (calculated from the formula: 1.988 s + 16°C × 0.106 s × $^{O}C^{-1}$) is comparable to values obtained in degassed distilled water phantoms at 37°C of 0.21 s^{-1} and 0.22 s^{-1} respectively on a 1.5 T system.[17,18] In the four Gd-containing solutions used, only the 0.5 mM phantom resulted in a regression slope significantly different from zero. The transversal relaxivity (r_2) was significantly reduced by pressure for all four Gd-phantoms, apparently

with an impact increasing proportionally with pressure (Table 3, Figure 4B). This finding is apparent from a graphical plot that shows the pressure-specific transversal relaxivity (r_2, $s^{-1} \times kPa^{-1}$) as a function of Gd-concentration (Figure 5B), demonstrating a negative regression significantly different from zero (Figures 4B and 5B).

Gaseous oxygen, unlike most other gases, is paramagnetic due to its two unpaired electrons and, thus, it has the potential to affect the magnetic properties of water in an MRI system in terms of R_1 and R_2.[19] The intermediate dipole-dipole interactions of oxygen molecules with protons should add a linearly dependent contribution to the relaxation rate in accordance with Solomon-Bloembergen equations.[20] Therefore, the method of degassing the Gd-phantoms in this study should be addressed. According to one study, 10–20% of the liquid is needed to evaporate during boiling under high vacuum to degas a solvent completely.[21] As described earlier, another method was employed in this study for practical reasons. Therefore, there could have been air (including oxygen) dissolved in the Gd-phantoms, having a potential contribution to both R_1 and R_2. Accordingly, minor differences in oxygenation between the phantoms could explain why the relaxivity of the 0.5 mM phantom was significantly modified by pressure, while the 0, 1.0 and 2.0 mM Gd-phantoms were not. Besides, because the T_2-weighted sequences are inherently susceptible to fluctuations in the magnetic field, diamagnetic gaseous oxygen leftovers from an incomplete degassing could explain why the transversal relaxivity is significantly affected by pressurisation for all phantoms.

The results from the phantom scans suggest that Eq. [1] and [2] may be discarded with the exception of CT imaging of compressible gases. In MRI, we found that an additional second-order term may be included for the R_2 relaxation rate, and Eq. [3] for R_2 should be modified as follows:

$$R_{2\,(P,[Gd])} = R_{2\,(P = 101\ kPa,\ \ [Gd] = 0)} + r_{2(P)} \times P + r_{2([Gd])} \times [Gd] + r_2' \times [Gd] \times P \quad [4]$$

Where r_2' is the first-order relaxivity constant for the combined pressure and gadolinium-concentration term. However, because the contribution of the pressure-modified transversal relaxivity to the resulting transversal relaxation is extremely small relative to the contribution from the imaged tissue (or phantom Gd-concentration), for pressures relevant to baro-physiologic and medical research, we believe that contributions from higher-order terms are small, and Eq. [3] would be a precise approximation to the transversal relaxation rate.

We found that no correction in image intensity was required for CT, PET or MRI up to a pressure of 1.013 mPa; that is, there were negligible effects of pressure per se on the signals obtained. However, for MRI, the signal modification associated with increasing oxygen tension of blood and tissues with pressure must be considered carefully. These findings represent a fundamental paradigm shift in barometric research, moving from imaging measurements before/after the pressurisation cycles to measurements performed during compression and decompression.

The described system could be useful for studies of physiological processes in live animals. However, some challenges remain. In particular, to avoided artifacts from movement, it is crucial that the animal stays perfectly still throughout the entire duration of a scan. However, because animals can rarely be trained to lie still for the duration of even shorter scans, anesthesia is often needed. Because CT, PET or MRI scans are not painful/harmful on their own, it is advantageous to use only very light anesthesia; especially during acquisition of physiological data that might be modified by anesthesia. It is beyond the scope of this study to discuss potential anesthesia methods, but we have promising preliminary experience from rodent experiments using intraperitoneal bolus injections of barbiturates (pentobarbiturate; 50 $mg \cdot kg^{-1}$) prior to pressure exposures. Furthermore, by fitting cannulas through pressure-tight cable penetrations it is possible to infuse fluids, providing a convenient route for administration of drugs and withdrawal of blood.

Conclusion

In conclusion, this study demonstrates a pressure chamber system compatible with CT, PET and MRI to collect morphological and physiological data non-invasively. Implementation of these advanced in-vivo imaging techniques in barometric research will provide new insights into fundamental mechanisms associated with acute direct and indirect effects of pressure exposure, including characterisation of haemodynamic effects and metabolic consequences in various tissues. We envisage that the described system could be of value for studies of the biological effects of gases in various fields, including: general anaesthesia;[22] inert gas narcosis;[23–25] oxygen toxicity;[26] gas poisoning (e.g., cyanide and carbon monoxide[27]); multiple indications treated with hyperbaric oxygen therapy[28–30] and differential pressure-related effects (e.g., the initial stages of the high pressure nervous syndrome[31] and DCS[32]).

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Acknowledgments

We thank Rene Wind and Hans Jørgen Hvid (Sjellerupskov, Denmark) for their enthusiastic technical assistance; Hans Erik Hansen and Thomas Hansen are acknowledged for help with custom-made adaptors and equipment crucial for the automatic pressure control system and Jonas L Andersen's assistance during the production of Figure 1. The Helga og Peter Kornings Fond supported the developmental phase of the system.

Conflicts of interest: nil

Submitted: 15 January 2015; revised 18 June 2015
Accepted: 17 August 2015

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Case report

Immersion pulmonary oedema and Takotsubo cardiomyopathy

Andrew Ng and Carl Edmonds

Abstract

(Ng A, Edmonds C. Immersion pulmonary oedema and Takotsubo cardiomyopathy. *Diving and Hyperbaric Medicine*. 2015 December;45(4):255-257.)

A 67-year-old female scuba diver developed a typical immersion pulmonary oedema (IPE), but investigations strongly indicated Takotsubo cardiomyopathy (TC). The cardiac abnormalities included increased cardiac enzymes, electrocardiographic anomalies and echocardiographic changes, all reverting to normal within days. This case demonstrates a similarity and association between IPE and TC, and the importance of prompt cardiac investigations both in the investigation of IPE and in making the diagnosis of TC.

Key words

Diving incidents; echocardiography; immersion; pulmonary oedema; cardiovascular; case reports

Introduction

Immersion pulmonary oedema (IPE) has been increasingly reported in the literature since the 1980s.[1] It can occur with surface swimming and scuba diving. The diagnosis is initially based on clinical criteria (i.e., onset of dyspnoea during diving, cough, frothy sputum, hypoxia and bilateral rales), confirmed by chest X-ray (CXR) or computed tomography (CT). Death or recovery occurs within hours. Recurrences are common.[2]

Takotsubo cardiomyopathy (TC) is an acute, reversible disorder of the heart characterised by left ventricular dysfunction. It is identified by echocardiographic evidence of transient apical ballooning, acute reversible apical ventricular dysfunction, transient electrocardiographic (ECG) changes and increased cardiac enzymes and markers despite normal angiography findings.[3,4,]

Case report

A 67-year-old woman developed respiratory distress whilst scuba diving near Wooli, NSW, Australia. She was an experienced diver with more than 1,800 dives over a 12-year period. She had never suffered a diving incident. Medically, she had spinal dysraphism and hypercholesterolaemia, both of which were well controlled on pregabalin and rosuvastatin. There was no evidence of hypertension, cardiac disease, arrhythmia or pulmonary disease. An echocardiogram during a routine medical check-up a year previously was normal. Cardiac CT calcium score at that time was 100 (1–10 = small plaque; 11–100 = mild plaque present; 101–400 moderate plaque; > 400 = extensive plaque).

On the day prior to the incident, she had two boat dives using compressed air, one to a maximum depth of 15 metres' sea water (msw) for 56 minutes and another to 18 msw for 48 minutes. Water temperature was 19^{O}C, which was colder than expected. There was a surge with a mild current and she was using hired equipment as she felt her own regulator had developed some resistance. All these factors made her more stressed than usual but she completed both dives with no symptoms. The next day, after a 21-hour surface interval (no appreciable nitrogen load), she performed a boat dive at 8:57 a.m. to 20 msw using her own regulator (the problem with resistance had been rectified). As the water temperature was still 19^{O}C, she added a wetsuit vest and an extra kg of weight (total 5.5 kg). The extra vest was described as tight but not overtly so. Sea conditions were mild, with minimal current and good visibility.

She had some initial difficulty with buoyancy and required a head-down descent. The dive was otherwise uneventful for 15 minutes. At that time and at a depth of 19–20 msw, she became aware of "*not feeling right*" and felt some difficulty in breathing. She indicated this to her companion and they ascended over 8 minutes to 5–6 msw where they performed a 5-minute safety stop. The dyspnoea worsened during this ascent and they then ascended rapidly to the surface, where she started coughing and expectorated pink, frothy sputum. She also felt a rattling sensation in her chest. There was no chest pain. At no time did she feel excessive resistance to breathing from her regulator and she did not remove her regulator until she reached the surface. There was no aspiration of sea water or bubbling in the regulator at any stage. Dive computer recordings revealed a surface-corrected respiratory minute volume of 12.4 L·min^{-1} compared to 16.2 L·min^{-1} the previous day. Her total dive time was 28 minutes.

From the surface, she was assisted into the boat, laid supine and given 100% oxygen by mask. On reaching the shore after approximately 40 minutes, she managed to walk from the jetty before being assessed by the ambulance and helicopter

retrieval crew. She was medivaced and admitted to Coffs Harbour Hospital within two hours of arriving on shore.

On admission, clinically she was in acute pulmonary oedema with crepitations to the mid zones bilaterally. Oxygen saturation on air was 90%. She was given 100% oxygen combined with continuous positive airway pressure, intravenous frusemide, aspirin, and clopidogrel. CXR showed acute pulmonary oedema. ECG revealed sinus rhythm, premature ventricular complexes, borderline left axis deviation and non-specific *t*-wave abnormalities on the lateral leads. Troponin T was elevated to 4,052 $ng \cdot L^{-1}$.

Transthoracic echocardiogram (TTE) was performed an hour after admission and showed normal left ventricular (LV) size with moderate segmental impairment of systolic function; left ventricular ejection fraction (LVEF) was 38%. There was extensive anterolateral, lateral and posterior hypokinesis and mild mitral incompetence. Four hours after admission, she underwent coronary angiography which revealed moderate segmental LV dysfunction (mid-anterior, lateral and inferoposterior hypokinesis with sparing of apex and basal walls). The left main coronary artery was widely patent, whilst the anterior descending, circumflex, intermediate and right coronary arteries had mild irregularities only. It was concluded she had minor diffuse coronary artery disease, not requiring any intervention. Haematological and biochemical results were normal. Natriuretic peptides were not performed.

She was well within six hours of admission and was discharged home the next day with a diagnosis of Takotsubo cardiomyopathy. She was taken off aspirin, frusemide and clopidogrel and was started on bisiprolol. A repeat TTE performed six days after the incident demonstrated normal LV and RV size and function; LVEF of 62%; Grade 1 (abnormal relaxation) diastolic dysfunction with normal estimated filling pressures with a normal estimated right heart pressures (RVSP = 34%) and mild (grade 1/4) mitral and tricuspid regurgitation.

She presented a week later for advice on returning to diving. On review of her clinical presentation, it was thought the likely diagnosis was IPE with TC. Pulmonary function testing was normal, with a forced expiratory volume in 1 sec (FEV_1) of 2.32 L, forced vital capacity (FVC) of 2.99 L and FEV_1/FVC ratio of 77%. Hypertonic saline provocation testing was negative. She was taken off bisiprolol and remained normotensive. On advice, she has refrained from further scuba diving and will take precautions while swimming/snorkelling.

Discussion

We describe a case of an elderly woman presenting with pulmonary oedema whilst scuba diving. Clinically she had typical IPE, but the cardiac investigations revealed characteristic evidence of TC. The important features that this case demonstrates are the similarity between the two disorders, the importance of early investigation if such cases are to be identified and the potential for false presumption of cardiac normality if these investigations are delayed.

There have been a number of proposed aetiologies for IPE, including cold-induced pulmonary hypertension, immersion, hydrostatic pressures, negative inspiratory pressures, exertion, stress, aspiration, genetic predisposition and underlying cardiac pathology. Other than immersion and possibly stress, most of the postulated causes for IPE were not evident in this patient. The better known diving disorders of aspiration, pulmonary barotrauma and decompression sickness were also not evident from the dive description or profile. There was no evidence, clinically or on investigation, of any respiratory or cardiac disorder preceding the dive or a week subsequently. The presence of known cardiac pathology in IPE cases has been noted previously.[5–9] More recently, there has been an association of IPE with transient cardiac pathology. Some divers with IPE present with findings of a reversible myocardial dysfunction (RMD); in at least 28% of cases in one series.[10]

Takotsubu cardiomyopathy is characterised by reversible left ventricular dysfunction.[3] It is more common in postmenopausal women. There is usually a trigger in the form of physical or psychological stress. Diagnostic criteria for TC require:

- transient LV wall motion abnormalities involving the apical and/or mid-ventricular myocardial segments with wall motion abnormalities extending beyond a single epicardial coronary distribution;
- absence of obstructive epicardial coronary artery disease or angiographic evidence of acute plaque rupture that could be responsible for the observed wall motion abnormality;
- new ECG abnormalities such as transient ST-segment elevation and/or diffuse T-wave inversions.[4]

There is typically a slight increase in the creatine kinase, troponins I and T and brain natriuretic peptide levels. The ECG, echocardiographic and ventriculographic changes resolve spontaneously. Reported mortality from TC has varied in different case series from 0 to 12%; overall in-hospital mortality was 1.1%.[11]

The abnormal investigations with RMD are similar to those of TC. The distinction between RMD and TC is ill defined and some regard these as interchangeable and expressions of stress cardiomyopathies.[3,4] Because the cardiac abnormalities are transient with TC/RMD, investigations need to be instituted promptly following the incident if such cases are to be correctly assessed.

Other cases of TC in scuba divers and swimmers have been reported.[12,13] Discussions on the appropriate first aid,

treatment and assessment for diving fitness are described elsewhere.[2] There are four possibilities to be considered when there is a co-existence of TC or RMD and IPE; either may lead to the other, IPE may be TC/RMD triggered by immersion or the association may be coincidental.

Conclusions

All cases of IPE should be investigated for possible TC/RMD as early as possible after treatment has been instituted. This includes cardiac enzymes and markers, ECGs and echocardiography. If any of these are abnormal, they should be repeated. Presumption of cardiac normality should not be made unless such investigations have been performed promptly. Normal investigations days or weeks later do not necessarily imply cardiac normality.

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Submitted: 01 May 2015; revised 09 September 2015
Accepted: 27 September 2015

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Critical appraisal

A single hyperbaric oxygen exposure preoperatively may modulate inflammatory markers and clinical complications following pancreatodudenectomy

Clinical bottom line:
1. Some evidence that hyperbaric oxygen (HBO) exposure modulates the levels of interleukin-6 (IL-6; down) and IL-10 (up);
2. Fewer pulmonary complications with HBO exposure but no difference in fistula development, bleeding or fever.

Citation:
Bosco G, Casarotto A, Nasole E, Camporesi E, Salvia R, Giovinazzo F, et al. Preconditioning with hyperbaric oxygen in pancreaticoduodenectomy: a randomised double-blind pilot study. *Anticancer Res*. 2014;34:2899-906.

Lead author's name and e-mail:
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Three-part clinical question:
Does preoperative hyperbaric oxygen exposure before pancreatoduodenectomy reduce the rate of postoperative complications?

Search terms:
Preconditioning; pancreatectomy; surgery

The study:
Double-blinded, concealed, randomised controlled trial with intention-to-treat.

The study patients:
Adult patients scheduled for pancreatoduodenectomy for pancreatic ductal carcinoma.

Control group:
(n = 11; 11 analysed)
A single sham exposure breathing air at 115 kPa for a total of 116 minutes on the day prior to surgery.

HBO group:
(n = 10; 10 analysed)
A single exposure to 253 kPa breathing 100% oxygen for a total of 116 minutes on the day prior to surgery.

The evidence:
See Tables 1 and 2.

Comments:
1. Small study, underpowered for some outcomes;
2. Statistically significant relationship between IL-6 and post-operative fistula; unclear if there is a causal relationship between serum IL-6 reduction and HBO exposure or between the development of fistula and serum IL-6 increase;
3. Reduction in post-operative pneumonia in HBO exposure patients should be confirmed in larger studies.

Appraised by:
Michael Bennett; Friday, 02 January 2015
E-mail: *<m.bennett@unsw.edu.au>*

Key words
Gastro-intestinal tract; surgery; hyperbaric oxygen; preconditioning; biomarkers; outcome; critical appraisal

Table 1
Clinical complications following pancreatoduodenectomy; HBO – hyperbaric oxygen; CI – confidence intervals

Outcome	Control group	HBO group	Relative risk	Absolute risk reduction	Number needed to treat or harm
Pulmonary complications	0.55	0	100%	0.55 (0.25 to 0.84)	2 (1 to 4)
Postop bleeding (95% CI)	0.18	0.30	-65% (-265% to 100%)	-0.12 (-0.48 to 0.25)	-8 (NNT = 4 to ∞) (NNH = 2 to ∞)
Postop fistula (95% CI)	0.27	0.33	-22% (-166% to 100%)	-0.06 (-0.45 to 0.33)	-17 (NNT = 3 to ∞) (NNH = 2 to ∞)

Table 2
Serum cytokine levels pre-operatively and one and seven days post-op;
* no units given (usually expressed as $pg \cdot ml^{-1}$); HBO – hyperbaric oxygen

Non-event outcomes	Time to outcome/s	Control group	HBO group	*P*-value
Serum cytokine IL-6 *	Pre-HBO / Post-HBO	5.97 / 24.06	5.06 / 5.81	
	Day 1 postop / Day 7 postop	179.54 / 24.5	141.23 / 21.76	0.009
Serum cytokine IL-10 *	Pre-HBO / Post-HBO	4.04 / 4.43	2.01 / 2.41	
	Day 1 postop / Day 7 postop	7.76 / 4.14	5.6 / 3.34	0.034

The world as it is

British Sub-Aqua Club (BSAC) diving incidents report 2014

Compiled by Brian Cummings, Diving Incidents Advisor

<www.bsac.com/core/core_picker/download.asp?id=26137&filetitle=Diving+Incident+Report+2014>

Summary of the 2014 report prepared by Colin Wilson

The BSAC started collecting and reporting on diving incidents in 1980, all of which data continue to be available.[1,2] There have been improvements in the amount and quality of information, and the incidents reported to them are audited to produce a useful annual report. Although these data are mainly from reports made by club members, other sources are also used.[3,4] Analysis of these reports has allowed the BSAC to identify common errors and mistakes leading to changes in training to reduce these errors. The reports have been summarised in this journal since 2006, with earlier reports detailing the data-collecting methods.[3,4]

As in previous years, the 2014 report covers the United Kingdom (UK) with a few reports by BSAC divers while overseas. There continues to be a decline in reports, with 216 incidents reported this time. This is over 40% lower than five years ago and the lowest number since 1992. There are fewer reports in all categories reported except the fatalities section. Decompression incident reports were much lower than for some years, with 57 cases of decompression illness (DCI). A caveat, as in previous years, is made that a number of the cases (41) reported in the "*diver injury/illness*" category are probably also cases of DCI.

In previous years, the ascent was identified as being a potentially dangerous phase of the dive, and fewer ascent reports (37) seem to support the benefit of appropriate, directed training to prevent these errors. Interestingly, it is noted that there were more incidents reporting malfunction of inflation or dump valves on a buoyancy compensation device (BCD) or drysuits. The involvement of the Coastguard, the Royal National Lifeboat Institute (RNLI) and Search and Rescue (SAR) helicopters were again all less than in previous years.

Fatalities

There were 16 fatalities recorded, close to the last 10-year average (15). BSAC members accounted for six of these. Unlike in other reports of diving fatalities,[5] the same quality and depth of information is rarely available and may make it difficult to ascertain a root cause, though in most cases an educated assessment can be made. It is also clear that more than one cause may be at play when things start going wrong.

Broadly the causes of these fatalities are similar to previous years with the analysis of the facts showing;

- Five cases (average age 60 years, compared to 42 years for fatalities from other causes) suffered a 'non-diving'-related medical incident (e.g., heart attack) while in the water.
- One additional case was probably medical.
- Four cases involved separation, which probably contributed to the outcome in two.
- In six cases, divers were diving in a group of three; in two cases separation occurred in low visibility.
- One case involved a snorkeller diving solo (a rare occurrence in UK waters).
- One case involved a rebreather diver being separated from a trio in poor visibility. It is unclear if the rebreather was implicated in the incident.
- One case involved diving to greater than 50 metres' sea water (msw) on open circuit where the diver made a rapid ascent, missing decompression.
- One case involved a diver breathing poisonous gas in a dry passage in a partially flooded mine.

Again, there is an increasing age in the fatalities section. The BSAC has analysed the age distribution of divers in 2013 compared to that of 16 years previously. In 1998, divers over 50 years of age represented 10% of the diving population and this had increased to 30% by 2013. Older divers should take account of the increased likelihood of a medical event when considering the type of diving in which they and their buddies engage. Accurate and honest reporting in medical self-declaration and subsequent follow up is important.

From the fatalities section:

Case 1

"A dive boat skipper called 'Mayday' 16 miles south of Beachy Head. He was heading to a diver who had surfaced and was unconscious. MRCC Dover immediately requested a helicopter from ARCCK and R-104 was tasked from Lee on Solent. A fishing vessel proceeded to the scene and the Trinity House vessel Patricia also proceeded. The dive boat reported nine other divers still down. The fishing vessel William approached from down tide and Patricia from up-tide. The boat then reported another unconscious diver had surfaced and he was working on both casualties with another diver leaving seven divers still down. R-104 evacuated the unconscious divers to Eastbourne hospital where they were declared deceased. The dive boat recovered the rest of the divers whilst the William and Patricia stood by and then proceeded back to Brighton marina. Sussex police informed and investigating. (Coastguard report). A media report of the pathologist's report put the cause of death in one case

as diffused gas embolism caused by pulmonary barotrauma and in the other case water inhalation."

Case 2

"An experienced cave diver had been exploring a disused quarry's cave and tunnel system with friends over the past year and was on a dive with two other cave divers. They had swum around 300m into a flooded tunnel to have a look at a dry passage. The diver left the water to explore the passage whilst his buddies waited by the water's edge. The diver turned around and was heard to say something about a problem with gas and then collapsed and fell back into the water. The buddies tried to resuscitate him but were unsuccessful and left to raise the alarm. Helicopter, mountain rescue and cave rescue teams were involved in the efforts to search for the diver and his body was recovered the following day by cave rescue divers. It was reported that the diver had been overcome by poisonous gas within the dry passage."

Decompression illness

There were 57 incidents of DCI reported, the lowest for many years. Analysis of the causal factors was similar to previous reports as follows:

- 25% repetitive diving;
- 23% rapid ascents;
- 19% diving to depths greater than 30 msw;
- 7% missed decompression stops;
- 7% involved repetitive dives with a reverse dive profile.

Some cases involved more that one factor. The content and order of this list is virtually identical to previous years.

From the DCI section:

Case 3

"A group of three divers conducted a dive on a wreck to a maximum depth of 24 m for a total duration of 36 min including stops of 1 min at 12 m, 1 min at 9 m and 3 min at 6 m. On returning to the boat all divers were well and showing no problems. Twenty min after surfacing one of the divers began feeling dizzy and sick and was monitored for 5 min during which time the symptoms worsened. The diver became breathless, lost balance and suffered from extreme fatigue and exhibited rapid eye movements. The Coastguard was contacted reporting a possible DCI. The Coastguard advised return to shore where the boat was to be met by an ambulance to transfer the diver to hospital. A rig safety ship offered assistance as they had a medic aboard and the diver was transferred to the safety ship, assessed and put on oxygen. The diver was then transferred to shore on the safety ship's rescue craft and taken to hospital by ambulance."

Case 4

"Two nitrox divers completed a 35 m dive for 42 min with a normal ascent and 8 min of decompression stops. About 90 min after surfacing one of the divers developed a rash across her shoulders and chest and then experienced visual disturbances and a headache. The diver was put on oxygen and the dive boat skipper alerted the Coastguard who scrambled a helicopter. The diver was airlifted to a hyperbaric chamber where she received recompression treatment. The diver recovered well after the treatment but a subsequent medical examination confirmed the diver had a PFO."

These annual reports indicate that the overall incidence of DCI is falling though sadly the number of fatalities remains the same. Common failures are repeatedly demonstrated in these reports and should help to direct education and learning. Thanks go again to the efforts of Brian Cummings and his team at the BSAC for collating this report. We must again acknowledge those who have honestly reported their failures and misdemeanours.

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Key words
Recreational diving; diving incidents; diving deaths; decompression illness; abstracts; case reports

Letter to the Editor

Cutis marmorata and cerebral arterial gas embolism

Dr Kemper and colleagues reported that, when air was injected into the cerebral circulation of pigs, they developed a rash that looked very similar to *cutis marmorata* of cutaneous decompression illness (DCI) and to *livido reticularis*.[1] They postulated that cutaneous DCI in divers may be centrally mediated as a result of cerebral gas embolism.

It would be helpful if Kemper et al. described the distribution of the rash in their pigs. In divers, cutaneous DCI is generally confined to parts of the body with significant amounts of subcutaneous fat, such as the trunk and thighs, and the rash often crosses the midline.

Colleagues and I have reported that cutaneous DCI is commonly associated with significant right-to-left shunts and particularly persistent foramen ovale (PFO).[2] We postulated that the manifestations of shunt-related DCI, whether neurological or cutaneous, are in large part determined by peripheral amplification of embolic bubbles in those tissues that are most supersaturated with dissolved nitrogen (or other inert gas) at the time that emboli arrive. Hence we postulated that cutaneous DCI is the result of amplification of gas emboli that invade cutaneous capillaries.

Dr Kemper has kindly sent me a number of the publications from his department on which their report of this skin rash in pigs is based. The aim of their experiments was to produce significant brain injury by means of cerebral air embolism. Their pigs had no tissues supersaturated with inert gas. They were ventilated with a F_iO_2 of 0.4 and anaesthetised with ketamine and midazolam. They were also given pancuronium and atropine, before air was injected into their cerebral circulation. If their findings in pigs and the resulting hypothesis were applicable to man, it would mean that one could get cutaneous DCI without decompression: one would only need cerebral gas embolism.

During contrast echocardiography, I have produced arterial gas embolism in many hundreds of patients with right-to-left shunts and it is certain that some bubbles went into their cerebral circulations, but I have never seen and no patient has reported getting a rash. Nor am I aware of any reports of gas embolism causing a rash like cutaneous DCI without there being tissue supersaturation following some form of decompression.

Kemper and colleagues injected between 0.25 and 1 $ml \cdot kg^{-1}$ body weight of air into the ascending pharyngeal artery (roughly equivalent to human internal carotid artery) of pigs weighing 30–40kg. That immediately produced significant elevation of blood pressure and heart rate suggesting a 'sympathetic surge'. This is similar to the haemodynamic effects that can occur with subarachnoid haemorrhage and some other catastrophic brain injuries. That effect may have been potentiated by pre-treatment with atropine. There was also a considerable increase in intracranial pressure and major adverse effects on cerebral metabolism. Some pigs died quickly and the survivors were killed at the end of the experiment. I suspect that no pig would have survived the experiments without major neurological injury if they had not been killed.

Most people with cutaneous DCI have no detectable neurological manifestations at the time that they have a rash. In those that do have neurological manifestations, it is rarely catastrophic.

The increases in heart rate and blood pressure reported in the pigs are similar to the effects of a phaeochromocytoma, which can cause *livido reticularis* in man.[3,4] Therefore, I wonder whether an alternative explanation for these observations might be that the cerebral injury in the pigs was so massive that the sympathetic surge was comparable to the effects of catecholamine release from a phaeochromocytoma and caused a rash similar to that seen in patients with a phaeochromocytoma.

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Key words
Cerebral arterial gas embolism; persistent foramen ovale; skin; decompression illness; letters (to the Editor)

Reply:

We would like to thank Dr Wilmshurst for his comments on our article.[1] The distribution of the rash in the animals in which it occurred was around the cheeks, neck and thoracic region as well as the abdomen and thighs. In our preliminary experiments there was a theoretical possibility of backflow of air directly from the catheter positioned in the ascending pharyngeal artery into the external carotid artery, resulting in a rash in the flow area of this artery, namely the head and neck.[2] In our later experiment, in which we used a balloon catheter, shunting of air to the extra-cerebral circulation was less plausible. The total volume of air injected in these experiments was a mean of 5.6 ± 1.3 ml, consisting of repeated injections of 0.2–0.5 ml.[3] As a result, some of these animals showed severe impact on cerebral metabolism (increase of intracranial pressure and brain lactate) and rashes on the abdomen and thighs. As we stated in our article, we cannot rule out the possibility of gas bubbles migrating through the brain circulation (due to the associated hypertension) and re-entering the systemic circulation, resulting in the skin manifestations, but we speculate that the rapid onset of the rash after the introduction of air suggests a centrally mediated response.

We agree with Dr Wilmshurst that the animals that survived the acute experiments, after recovery from anesthesia, could possibly have had severe neurological deficits. In addition, based on results in our latest study, we also make a plea for improving the model by introducing clinical outcome measures.

Dr Wilmshurst questioned whether a systemic surge of catecholamines due to severe cerebral injury might be an alternative explanation for the observed rash, as seen in phaeochromocytoma patients. We agree with this hypothesis and postulate a mechanism in which bubbles or bubble-related effects give rise to the release of neuropeptides or catecholamines which, in turn, result in an inflammatory response in the skin. This possible mechanism has been described earlier[4,5] and very recently hypothesised in another paper in which it is speculated as a disruption of the brainstem vasomotor response by bubbles.[6]

In conclusion, although we cannot exclude recirculating bubbles resulting in peripheral skin embolization in our animal model, the hypothesis on cerebrally mediated *cutis marmorata* is plausible and needs further research to elucidate the exact mechanism.

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Key words
Cerebral arterial gas embolism; persistent foramen ovale; skin; decompression illness; letters (to the Editor)

Book reviews

Deep into deco: the diver's decompression textbook

Asser Salama

Softcover or eBook format, 120 pages
ISBN 978-1-930536-79-1
North Palm Beach FL: Best Publishing Company, 2014
E-mail: <info@bestpub.com>
Available from: http://www.bestpub.com
Price: softcover USD$29.99; eBook USD$19.99; package softcover + eBook USD$39.99

Deep into deco is introduced by the publisher as a comprehensive, up to date and easy to understand reference text covering various topics of decompression theory for all divers. The target audience is intended to be divers with an interest in applied decompression physiology. Author Asser Salama is a technical diving instructor and software developer with an interest in decompression modelling. He publishes a quarterly online magazine *Tech Dive Mag*, which collates contributions from the online technical diving community. He has built decompression software that he markets under the name *Ultimate Planner*.

The softcover version is a modest 120 pages, professionally laid out, that makes good use of relevant and interesting illustrations. The writing style is generally clear and concise. The first two chapters summarise achievements of the early pioneers of diving physiology, and provide a basic primer on the principles of decompression physiology. Salama then introduces dissolved gas models, followed by two chapters discussing nitrox and mixed gases, then returns to discuss bubble models in chapter six. Chapter seven briefly reviews probabilistic and diffusion models before chapter eight valiantly attempts to cover everything else from the oxygen window to omitted decompression to the unusual theory of washout treatment.

It would be an impossible task to thoroughly address such a wide range of topics in such a small volume, and inevitably some areas suffer from a lack of balance. For example, under the heading '*Novel Approaches*', Madden & Laden's 2009 paper[1] is referenced to support the controversial contention that bubbles may not be the cause of decompression sickness (DCS). The fact that this paper presented an unproven hypothesis for debate and further investigation was not mentioned, and the lack of more recent follow-up research is telling. A more balanced appraisal of the literature on this subject would have acknowledged the overwhelming weight of scientific opinion and research on decompression stress, recognising intravascular bubble numbers as highly significant, despite the well-known difficulty in correlating bubble numbers and the incidence of clinical DCS.

The book devotes significant space to detailed descriptions of how decompression algorithms can be manipulated to produce novel results. An example of this is the discussion on 'accelerated no fly times' following use of surface oxygen. While such discussions give insight into the programming logic that can be used to produce operational decompression algorithms, they also give an impression of the author playing with numbers. Discussion around the limitations of data used to derive and validate the original tables is limited and the reader is left with the sense that the results of such software tweaks, while mathematically interesting, have little or no supporting empirical evidence. Some may also find the frequent references to the author's own software product to be excessive.

Describing *Deep into deco* as a textbook is to overextend the definition given the conversational style, relative brevity and lack of an index. We felt it was heavy on anecdote in places, and while the author references some of his assertions, many of those made by the interviewed contributors are left for the reader to either accept at face value or research further themselves. We found the frequent inclusion of interview extracts to be one of the most interesting features of the book, and enjoyed reading the summarised opinions of a number of divers, explorers and researchers on topics ranging from the validity of certain decompression algorithm assumptions through to narratives of historical deep exploratory dives.

Where topics are introduced in one chapter, partially explored, then concluded in later chapters the reader can be left with a sense of disjointedness. For example, deep stops are discussed in chapter three, but the more recent studies which have seriously questioned their effectiveness are not addressed until chapter eight. When combined with the lack of an index, this can make finding specific topics challenging.

This book addresses a complex topic and succeeds in providing a broad overview of the historical and some of the more recent research into decompression modelling. While we do not completely agree with all of his conclusions, we found *Deep into deco* to be a thought-provoking, relatively up-to-date dissertation on applied decompression physiology from a software engineer's perspective.

Reference

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Key words
Decompression; decompression tables; computers - diving; models; book reviews

The Science of Diving

Costantino Balestra, Peter Germonpré, editors

Miroslav Rozloznik, Peter Buzzacott and Dennis Madden, co-editors
272 pages
Saarbrücken: Lambert Academic Publishing, 2014
ISBN 978-3-659-66233-1
Available from: <https://www.morebooks.de/store/gb/book/the-science-of-diving/isbn/978-3-659-66233-1>
Price: EUR€49.90

This recently published book edited by Balestra and Germonpré, both faculty members at famous institutions in Bruxelles (Belgium), also lists as co-editors Miroslav Rozloznik, Peter Buzzacott and Dennis Madden, all members of the European Underwater and Baromedical Society. The tantalizing subtitle: "*Things your instructor never told you*" promises practical details and useful pearls not commonly described or available in a physiology compendium. However, the technical minutiae are not evenly distributed in the text and need to be found on your own, since they are scattered in various places. In fact, the contents cover the traditional gamut of applied diving physiology concepts and evaluation of diving risks, with the novel approach that they are estimated from recent databases assembled from the diving public, especially recreational divers.

The titles of the chapters are modern and appear in a logical sequence, as the text covers classical concepts and physiological factors of personal susceptibility. However, the authors of the individual chapters are groups of 'experienced researchers' and 'early-stage researchers', young trainees in process of gaining experience while completing their post-graduate research: these latter scholars are applying their work experience to add a new view to traditional physiological principles. Hence there is a novelty to the contents, especially the tables and figures that are richly distributed throughout the text. The groups originally worked in their native languages, and only later produced a final English text. This idiomatic variety produces diverse styles and varies the reading pace throughout the book. Also the quality of separate chapters varies to a high degree, with superb synthesis in some areas and concepts still in raw development in others.

After multiple book introductions and front-matter details the book opens with three chapters describing the three populations at risk of diving diseases: the sport and recreational diver (chapter 1); the advanced technical diver (chapter 2) and the commercial diver (chapter 3). The databases describing diving profiles and risks of decompression sickness (DCS) are principally collected from the DAN Europe Diving Safety Laboratory (DSL) database of approximately 40,000 profiles. This is a comprehensive list of epidemiological data, breathing gas used, equipment malfunctions and medical history recorded using a specific questionnaire. Today's divers are quite sophisticated; scuba diving remains a relatively safe activity and decompression incidents are often not related to exceeding safe M values, the crucial variable estimating inert gas supersaturation levels for different tissues at different time points. Interestingly, in only 10% of reported DCS cases were the maximum recommended supersaturation levels approached. Indeed, most often DCS is reported when M values are below 80% of safe maximums. Therefore, there must be multiple personal additional factors involved for a reported DCS, besides 'safe' M values. For example, the level of hydration is most important: hyper-hydration preceding a dive reduces bubble scores. Today, even recreational divers use diving computers; several European models are listed and compared, and a large variability is observed when similar immersion profiles are simulated, leading to more than a 30% variation in estimating decompression times amongst the diverse models and opening an interesting discussion on the need and complexity of validating dive computer accuracy and obsolescence.

Chapter 2 describes the improvement in equipment and extension of breathing gas mixtures available to the advanced diver 'going tech'. These implements often extend the limits of risk rather than providing a safer environment. Development of rebreathers, availability of tri-mix breathing mixtures or enriched-air nitrox, closed-circuit rebreathers, better insulated drysuits with additional passive protection or active electrical heating systems can extend the depth and duration of diving, while maintaining acceptable limits to oxygen toxicity and reducing decompression times. Additional complexities are also added, such as multiple-dive days and multiple-days diving, often followed by flying after diving.

Commercial divers (chapter 3) are regulated into more conservative and safe limits and their activities are not frequent: recently, only approximately 1,000 dives per year were completed in the North Sea. The appropriate use of checklists and the various ways to extend practical decompression limits with in-water decompression, surface decompression, bell bouncing and saturation exposures are described and illustrated.

Chapter 4 enters into the evolution of calculations for inert gas loading in tissues during exposure to increased pressures: from Haldane to Workman to Bühlmann formulae and the concepts of 'silent' bubbles and 'deep stops'. The firm principle is that the total volume of inert gas which needs to be expelled during decompression depends solely on the gas gradient x time available x number of bubbles formed. This opens the discussion to supersaturation nucleation and highlights a crucial observation on bubble counts: venous gas bubble counts are significantly higher for in-water diving compared to an equivalent dry-chamber exposure. Here the concept of the 'oxygen window' is introduced and illustrated.

This chapter is complex and presents the evolution of modern theories of decompression; the introduction, however, makes for some light reading, rather like an airline magazine story. However, the body of the chapter is solid and restores the physiological tone.

Chapter 5 focuses on a relatively new physiological variable: the endothelium as a crucial tissue which is altered by diving, and the new tests available to evaluate its limits via post-ischaemic vascular reactivity. Endothelial metabolism is altered by pressure and oxygen exposure and the return to normal, after elevated pressure exposure is delayed by minutes to hours.

Chapter 6 has a more familiar theme dedicated to bubble evaluation and counting systems and techniques. Doppler types and scales of estimating the number and distribution of venous bubbles are explained and lavishly illustrated.

Chapter 7 explores preconditioning tools and manoeuvres to stay in good physical shape, the effect of pre-dive exercise, hydration, hot environments, body vibration and pre-oxygenation concepts, all of which might potentially bolster safety by reducing DCS risk.

In chapter 8, persistent foramen ovale (PFO) and pulmonary shunts are discussed, leading to arterialization of bubbles and possible acute and/or more subtle effects; the diagnosis of a PFO does not exclude the subject from diving, but will require limitations to depth and exposure and possibly avoidance of exercise for several hours after diving.

Chapter 9 describes inert gas narcosis and the impairment to a diver's ability to function effectively: importantly, this cerebral impairment has been difficult to quantify but its effects appear to last for several minutes to hours after surfacing: tolerance to nitrogen narcosis does not develop but coping with it does and can be learnt, to avoid major complications.

Chapter 10 describes various classifications of DCS and its multiple manifestations and symptoms. Several scales of evaluation are presented, in addition to the classical division between AGE, Type l DCS and Type ll DCS. This discussion leads to the concept of 'cluster analysis' of symptoms which could allow hierarchical ordering of symptom clusters with increasing levels of severity, likely to elicit different treatment options and levels of intervention: this could herald automated treatments in austere situations.

Finally, chapter 11 describes the complexities of decision making for treatment of DCS in remote locations and the attendant risks of omitted treatment in the many cases of denial. In remote locations, few alternatives may be available to the stricken diver with no reasonable transport available to a local chamber or more distant medical hyperbaric facility, lack of supplies and gases or oxygen for treatment. In-water recompression and extended stops could conceivably help. Phone assistance and evacuation strategies have been codified and the organization of services is improving. Considerable uncertainty remains in the evaluation of return to diving for the diver who was 'hit' and variously treated.

In conclusion, this textbook is highly recommended: the interest of the reader is kept high by the diversity of styles and the originality of the figures. Overall, the concepts and evidence presented are new, the reading is pleasant and leads to new vistas not previously imagined by physiologists and physicians familiar with the US Navy Diving Manual.

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Key words
Diving research; decompression sickness; decompression; endothelium; persistent foramen ovale; narcosis; book reviews

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The Science of Diving

Support EUBS by buying the PHYPODE book "*The science of diving*".

PHYPODE research fellows, <www.phypode.org>, have written a book for anyone with a keen interest in the latest research trends and results in diving physiology and pathology. Edited by Tino Balestra and Peter Germonpré, the royalties from this book are being donated to the EUBS. Need more reason to buy? TB and PG don't think so!

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Oxygen and the brain; the journey of our life time

Philip B James

Softcover or eBook format
516 pages
ISBN 978-1-930536-50-0
North Palm Beach, FL: Best Publishing Company, 2014
Available from: <http://www.bestpub.com>
Price: softcover USD$49.99; eBook USD$33.50; package of both USD$69.00

Being a reviewer is both challenging and rewarding, as I found out when trying to review this rather extraordinary book; it was no easy task! There is no doubt that the author has considerable knowledge about oxygen, in particular the use of hyperbaric oxygen (HBO). In my opinion, it also clearly shows that the author has considerable bias regarding this. All through the book we find statements like "*oxygen is not a poison*", "*free radicals are the latest fashion*" and "*controlled trials are not needed*". James wishes to dispel "*the myth surrounding oxygen that is impeding progress*". For many reasons, I do not believe that this book will contribute to this.

When all is said, the book does contain much interesting data and thoughts. Its main theme is that oxygen does not have the important role that it deserves in medicine. One has the impression that oxygen is good for you, regardless. One might disagree with that but it is indeed remarkable that, in spite of the fact that oxygen is used by nearly all doctors, remarkably little is known about it and its optimal dosage and timing, in particular when oxygen is available at increased environmental pressure.

The more than twenty chapters range from space to the deep seas and, in between, he discusses a considerable number of medical problems, from decompression sickness to multiple sclerosis (MS), to head injury and sports injuries. Throughout, the author claims that the central problem in all these diseases is a lack of oxygen. This reminds me of the saying "*to all problems there is a simple solution, but it is wrong*"(with apologies to HL Mencken[1]). James argues well for the use of oxygen, but in the few cases where oxygen does not give the expected positive results, he claims that the dosage or timing is wrong. I think he would have a stronger case if he had been somewhat more modest and selective in his approach.

The author has considerable experience in using oxygen at high pressure and has met considerable resistance when trying to introduce HBO in medicine, for instance, for treating MS, brain injury and autism. There is no doubt that he considers this book to be the final word in the debate on HBO, in particular, in treating diseases of the central nervous system.

James obviously feels there is a conspiracy against the use of oxygen; "*oxygen has a bad press*". One has the feeling that, when arguing for the increased role of HBO, he is his own worst enemy. Regrettably HBO is regarded still by most medical doctors as 'alternative medicine'. It is indeed remarkable that the accepted indications for such treatment have not increased over many decades. This does not mean that HBO cannot be the treatment of choice in many more cases than for its traditional uses. I think the main reason for this is that there is a considerable lack of good, published scientific studies.

The author advocates strongly for HBO to treat MS. Contrary to the author, I think that the reason for the resistance against HBO treatment for MS is that we have no good model for the pathophysiology of the disease; oxygen may be involved but this might not be the whole story. However, it is worth contemplating the stories about the resistance against HBO and pondering the comment that "*medicine is not kind to whistle-blowers*".

I have known the author for many years and I hope that this review will not lead to a lengthy discussion for and against HBO. James and I share a deep respect for Haldane and for his contribution to environmental medicine, which also is highlighted in this book. I can understand that the author feels very strongly against those who do not agree with him and he seems to compare himself to the large number of pioneers in medicine who, in spite of opposition, fought against established wisdom. He is saying to us, our time will come, and he may well be right.

Reference

1 Wikiquote [Internet] *H.L. Mencken*. [cited 2015 November 08]. Available from: https://en.wikiquote.org/wiki/H._L._Mencken

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Key words
Hyperbaric oxygen; central nervous system; decompression sickness; multiple sclerosis; injuries; book reviews

Continuing professional development

Women in diving

Jagoda Szkurlat

Accreditation statement

INTENDED AUDIENCE
The intended audience consists of all physicians subscribing to *Diving and Hyperbaric Medicine* (DHM), including anaesthetists and other specialists who are members of the Australia and New Zealand College of Anaesthetists (ANZCA) Diving and Hyperbaric Medicine Special Interest Group (DHM SIG). However, all subscribers to DHM may apply to their respective CPD programme coordinator or specialty college for approval of participation.

This activity, published in association with DHM, is accredited by the ANZCA Continuing Professional Development Programme for members of the ANZCA DHM SIG under Learning Projects: Category 2/Level 2: 2 credits per hour.

OBJECTIVES
The questions are designed to affirm the takers' knowledge of the topics covered, and participants should be able to evaluate the appropriateness of the clinical information as it applies to the provision of patient care.

FACULTY DISCLOSURE
Authors of these activities are required to disclose activities and relationships that, if known to others, might be viewed as a conflict of interest. Any such author disclosures will be published with each relevant CPD activity.

DO I HAVE TO PAY?
All activities are free to subscribers.

Key words
Women; diving; decompression illness; pregnancy; implantable devices; risk factors; MOPS (maintenance of professional standards)

Recommended background reading

Practitioners are referred to the following background references and reading.

1 McNamee K, Harvey C, Bateson D. A practical guide to contraception. Part 1: Contraceptive pills and vaginal rings. *Med Today*. 2013;14(7):18-32.
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10 St Leger Dowse M, Gunby A, Phil D, Moncad R, Fife C, Morsman J et al. Problems associated with scuba diving are not evenly distributed across a menstrual cycle. *J Obstet Gynaecol*. 2006;26:216-21.

How to answer the questions

Please answer all responses (A to E) as True or False.
Answers should be posted by email to the nominated CPD coordinator.
EUBS members should send their answers to Lesley Blogg.
E-mail: <lesley.blogg@eubs.org>
ANZCA DHM SIG and other SPUMS members should send their answers to Neil Banham.
E-mail: <Neil.Banham@health.wa.gov.au>
If you would like to discuss any aspects with the author, contact her at: <j.szkurlat@doctors.org.uk>.

On submission of your answers, you will receive a set of correct answers with a brief explanation of why each response is correct or incorrect. A correct response rate of 80% or more is required to successfully undertake the activity. Each task will expire within 24 months of its publication to ensure that additional, more recent data has not superseded the activity.

Question 1. The advice below should be discussed with female divers:

A. diving should be avoided if pregnancy is suspected or planned;
B. the Mirena® is contraindicated in women divers who suffer from migraine with aura;
C. the failure rate of typical male condom use is 18%;
D. severe premenstrual dysphoric disorder might disqualify one from being fit to dive;
E. diving with silicone breast implants is not advised due to the risk of rupture secondary to bubble formation inside the implant.

Question 2. Women divers who use oral combined hormonal contraception:

A. should consider another form of contraception if they are over age 35 and smoke more than 15 cigarettes a day;
B. and have a history of migraine, but no attacks in the last 5 years, fall within category 4 for stroke risk according to the WHO Medical Eligibility Criteria for Contraceptive use;
C. have four to five times the risk of venous thromboembolism compared with non-users if they use a low oestrogen dose pill;
D. should be aware that seasickness and gastroenteritis might make oral contraception less effective;
E. always require emergency contraception if they take the oral contraceptive pill more than 24 hours late and have had intercourse within the last five days

Question 3. If a woman dives whilst pregnant:

A. the placental circulation protects the fetus from bubble formation;
B. there is conclusive evidence that this increases the risk of human birth defects, stillbirth and spontaneous abortion;
C. she should be counselled to terminate the pregnancy due to the above;
D. it is safe to give her hyperbaric oxygen should she suffer from DCS;
E. she should dive to less than 20 m depth and halve the recommended table/computer dive duration.

Question 4. The following advice should be given to women wanting to dive postpartum:

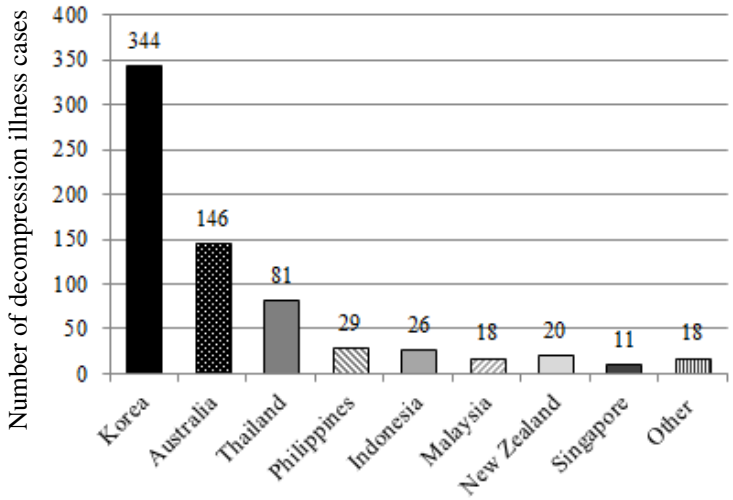
A. following uncomplicated vaginal delivery it is safe to resume diving after 14 days;
B. the cervix takes 28 days to close;
C. most obstetricians recommend waiting 4–6 weeks prior to immersion after a Caesarian section;
D. diving is not recommended if breastfeeding, due to the nitrogen dissolved in breastmilk;
E. post-natal mental health and anaemia need to be stable prior to diving again.

Question 5. Being female predisposes women divers to:

A. more dive-related injuries to the shoulder and neck compared to male divers;
B. attracting sharks when menstruating;
C. the same risk of suffering from nitrogen narcosis as male divers;
D. a variation of risk of diving incidents depending where they are in their menstrual cycle;
E. an increased risk of DCS compared to male divers due to their relatively higher percentage of body fat.

Decompression illness by country and overall diving fatalities reported in the Asia-Pacific region for 2013

DAN Asia-Pacific (DAN AP) received reports of 693 recreational divers being treated for decompression illness in the region in 2013 (see figure), based on reports received from the major chambers; however, there are small chambers in some countries from which DAN AP receives no reports. The disproportionately high number from South Korea is unexplained and could indicate a safety issue, a low threshold for treatment or an issue with the reporting of the information. There were 64 fatalities reported, but these data are probably somewhat unreliable. These data are taken with permission from *Alert Diver*. 2015;Quarter 2:4.



The world as it might (possibly) be

Correlation of wavelength and amplitude of visual peripheral stimuli with decompression sickness in 'teckies': a triple-blinded, power-analysed study

Arne 'Santa' Sieber, Lesley 'Prancer' Blogg, Ingrid 'Dancer' Eftedal and Andreas 'Rudolph' Møllerløkken

Introduction

Research on decompression models is shifting away from traditional physical and statistical approaches towards those that include physiological parameters, such as 'Copernicus' and the 'digital diver'.[1] Endothelial function, genetic disposition and heart rate, for example, are all currently being investigated.[2–6] Although visual stimuli have been used to assess narcosis and oxygen toxicity, any correlation of this parameter with decompression sickness (DCS) occurrence has not been investigated.[7] The present paper reviews DCS occurrence in 'teckies' and investigates any correlation with peripheral visual stimuli in the diver.

Methods

A questionnaire was sent to 251,214 technical divers of both sexes, with a minimum of 1,000 hours of diving logged. The questionnaire examined the type of optical adjustment systems used by each diver and asked if they had ever been diagnosed with DCS.

Peripheral visual stimuli are dominated by the reflectance spectrum of the diver's optical adjustment system. An optical densitometer was used to measure reflectance in all of the optical adjustment systems that are available on the market. The reflected light was analyzed with a spectrometer in a range between 450 and 780 nm. The results were logged, then compared with the responses given in the questionnaires.

Results

Response and return of the questionnaire was 100%. Of all divers polled, 99.99% used an optical adjustment system with a reflectance at the lowest end of the scale. The typical reflectance spectrum of an optical adjustment system was below 10%. The reflectance spectra are even, with no differing wavelengths bar one small peak at the upper end of the scale. This indicates that most optical systems used were black (Figure 1). Twenty-five divers (0.01%) used an optical system that registered at the higher end of the reflectance spectrum. This equated to a pink colour (Figure 2; sorry B&W only). Twenty-four of these respondents were female (age range 18–22 years), the other was an older Scandanavian male known to the authors.

In total, 3,768 teckies had been diagnosed or treated for DCI; 1.5% of the polled population, in keeping with previous studies of DCS in a similar group.[8] All divers with DCI used a black optical adjustment system ($P < 0.0001$).

Figure 1

Figure 2

Discussion

There was a very strong correlation between DCS occurrence and a low level of optical reflectance, i.e., the mask was black. Of the small population that wore optical systems with spectral reflectance at the higher end of the scale, no cases of DCS were observed; therefore, it can be said with some confidence that brightly coloured optical systems, especially pink ones, are protective for DCS.

One particular case was investigated. This female diver (known to many in the baromedical diving community) was wearing a mask with a typical low optical reflectance but also a strikingly coloured wetsuit with multiple spectral spikes at the wavelengths corresponding to bright blue, green, orange and pink. In a typical diving position, the diver is looking forward and peripheral stimuli coming from the suit are outside the field of vision. Therefore, we conclude that the colour of the suit has no protective effect against DCS.

Conclusion

Being a teckie diver is risky; DCS can occur despite the use of modern decompression strategies that are considered 'safe'; decompression is still not completely understood. This investigation shows clearly that the color of the optical adjustment system, or 'diving mask', may increase the risk of DCS. In other words, using a brighter, more colourful (preferably pink) mask for technical diving is likely to reduce the risk of DCS. This might also explain why many tropical fish are so brightly coloured. Therefore, the authors have

contacted Santa Claus asking him to bring bright, colourful diving masks for teckies the world over.

We wish you "*Merry Christmas and a successful, safe and healthy 2016!*"

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Conflict of interest

Any resemblance of the authors to real persons is purely coincidental. All the references are genuine and well worth reading!

Key words
General interest

Erratum

In the paper:
Smart DR, Van den Broek C, Nishi R, Cooper PD, Eastman D. Field validation of Tasmania's aquaculture industry bounce-diving schedules using Doppler analysis of decompression stress. *Diving and Hyperbaric Medicine*. 2014 September:44(3):124-136.
numbering in the reference list starts at 3, whereas it should start from number 1. The numbering sequence in the text is correct.

Back articles from DHM

After a one-year embargo, articles from *Diving and Hyperbaric Medicine* (DHM) are placed in the public domain on the Rubicon Foundation website:
<www. http://rubicon-foundation.org/>.
This is an open-access database, available free of charge and containing many thousands of other publications. At present, this is not fully up-to-date for DHM but articles to the March 2012 issue are currently available. All articles to end 2014 should be on-line soon.

Rubicon seeks donations to support its work to document the diving and hyperbaric scientific literature.

More recent articles or other enquiries about articles should be sent to: <editorialassist@dhmjournal.com>. Embargoed articles will be charged for – fee on application.

Complete back issues of DHM may be purchased from the SPUMS administrator at: <admin@spums.org.au>

SPUMS Diploma recipients since 2014 AGM

The following seven SPUMS members are to be congratulated for having been awarded their Diploma of Diving and Hyperbaric Medicine since the 2014 AGM:

Elizabeth Elliott: The assessment and management of inner ear barotrauma in divers and recommendations for returning to diving. *Diving Hyperb Med*. 2014;44:208-22.

Marco Gelsomino: Development and testing of a pleural vacuum relief device to allow normalised pressurisation rates and minimal staff input when pleural drain units are used in the hyperbaric environment.

Iestyn Lewis: Performance of the Baxter Infusor LV10 under hyperbaric conditions. *Diving Hyperb Med*. 2014;45:37-41.

Csongor Oltvolgyi: Subatmospheric decompression illness: a review of aetiology, clinical presentation, and treatment.

Alexander Pullen: A survey of illicit drug use amongst Western Australian recreational divers.

Michael Reid: Decompressing rescue personnel during Australian submarine rescue operations.

Susannah Sherlock: Hyperbaric oxygen therapy in the treatment of sudden sensorineural hearing loss: a retrospective analysis of outcomes and narrative review of alternative therapies.

Notices and news

SPUMS notices and news and all other society information is now to be found mainly on the society website: <www.spums.org.au>

SPUMS Annual Scientific Meeting 2016

Diver resuscitation: in and out of the water

Dates: 15–21 May
Venue: Intercontinental Fiji Golf Resort and Spa, Natadola Coast

Keynote speaker: Chris Lawrence, Forensic Pathologist, Hobart, Tasmania
Other speakers: Simon Mitchell, John Lippmann, Mike Bennett
Workshop: A diving-focused Advanced Life Support Course (recognised for CME points)

Convenor: Janine Gregson <asm2016@spums.org.au>
Full information is on the SPUMS website
Follow along @
Facebook: www.facebook.com/spums2016
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The conference is already heavily booked, so register now!

Australian and New Zealand College of Anaesthetists Certificate in Diving and Hyperbaric Medicine

As you may be aware, the ANZCA Certificate in Diving and Hyperbaric Medicine (DHM) is currently under review. ANZCA has not been accepting new trainee registrations since 01 August 2013 and this situation will continue until the Working Party recommendations have been finalised. The Diploma of DHM that is organised by the South Pacific Underwater Medicine Society (SPUMS) is not included in the review.

In accordance with a recommendation from a previous ANZCA Working Party, trainees who were registered for the ANZCA Certificate DHM before it was put on hold (i.e., prior to 01 August 2013) are able to complete and sit the examination. ANZCA has confirmed examination dates for 2016.

To be eligible to sit the above mentioned examination(s), candidates must have:

- Been registered with ANZCA for the DHM certificate prior to 01 August 2013 and paid all relevant fees;
- Successfully completed a Fellowship with a specialist medical college recognised by ANZCA Council (e.g,. FANZCA, FACEM, FCICM);
- Achieved the SPUMS Diploma of Diving and Hyperbaric Medicine or The University of Auckland Postgraduate Diploma in Medical Science – Diving and Hyperbaric Medicine or equivalent;
- Completed their workbook and/or formal project (for the Auckland diploma this is having completed either MED718 or MED719 as part of the course).

Please note that documentation of the above must be received by ANZCA on or before the closing dates of the nominated examination to allow verification by a DPA Assessor.

Periodic updates on the review of the DHM Certificate will be made available on the ANZCA website. All interested parties are advised to regularly visit the webpage <http://www.anzca.edu.au/training/diving-and-hyperbaric-medicine> to ensure you are kept up to date.

For further information contact: <dhm@anzca.edu.au>.

2016 examination dates for the ANZCA Certificate in Diving and Hyperbaric Medicine examination

Closing date for exam registration	Friday 22 April	Friday 09 September
SAQ examination	Friday 10 June	Friday 04 November
Oral viva examination	Friday 15 July	Friday 02 December

SPUMS Diploma in Diving and Hyperbaric Medicine

Requirements for candidates (May 2014)

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

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

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

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

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

Additional information – prospective approval of projects is required

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

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

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

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

As of 01 June 2014, projects will be deemed to have lapsed if

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

With respect to 1 above, for unforeseen delays where the project will exceed three years, candidates must advise the Education Officer in writing if they wish their diploma project to remain active, and an additional three-year extension will be granted.
With respect to 2 above, if there are extenuating circumstances that a candidate is unable to maintain financial membership, then these must be advised in writing to the Education Officer for consideration by the SPUMS Executive.

If a project has lapsed, and the candidate wishes to continue with their DipDHM, then they must submit a new application as per these guidelines.

The Academic Board reserves the right to modify any of these requirements from time to time.
As of January 2016, the SPUMS Academic Board consists of:
Dr David Wilkinson, Education Officer, Adelaide
Associate Professor Simon Mitchell, Auckand
Dr Denise Blake, Townsville.

All enquiries and applications should be addressed to:
David Wilkinson
Fax: +61-(0)8-8232-4207
E-mail: <education@spums.org.au>

Key words
Qualifications; underwater medicine; hyperbaric oxygen; research; medical society

Notices and news

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

42nd EUBS Annual Scientific Meeting 2016

Dates: 13 – 16 September
Venue: Geneva, Switzerland

Save the date for the next appointment with our friends from all around Europe to talk about diving and hyperbaric medicine. It will be the occasion to improve and update our knowledge with the latest studies and research in the field. Speakers and guests will be welcomed in the international conference centre in Geneva (CICG), the perfect place for our annual scientific and social meeting.

For any inquiries, please contact the congress secretariat at: <eubs2016@ch.kuoni.com>

Zetterström Award 2015

The Zetterstrom Award Committee consisted of P Westerweel and T Van Rees Vellinga for the local Scientific Committee and P Bryson and C Balestra for the EUBS ExCom. The recipient for 2015 is:

Mariana Cervaens, et al. Effects of hyperbaric therapy on rat skeletal muscle mitochondrial swelling induced by contusion.

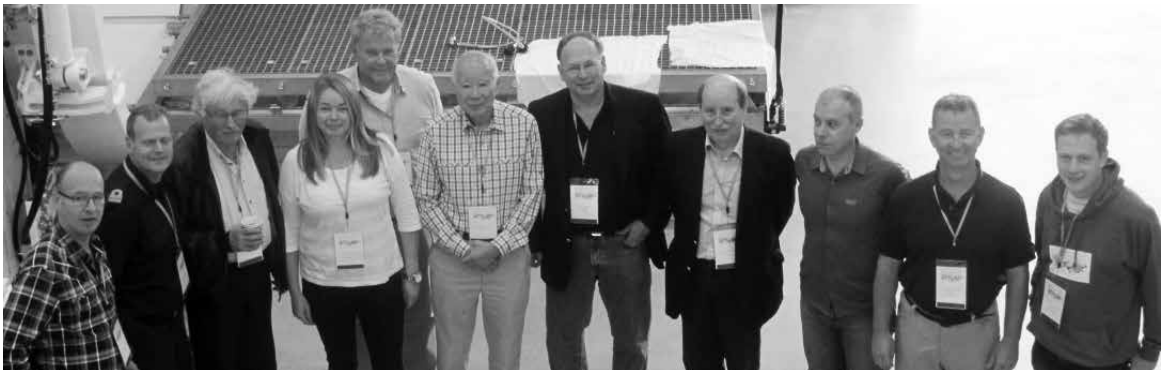
Ultrasound 2015 Meeting report

The inaugural International Meeting on Ultrasound for Diving Research (Ultrasound 2015) was convened by Lesley Blogg and Andreas Møllerløkken. It took place at the Swedish Armed Forces Diving and Naval Medicine Centre (DNC), Karlskrona, Sweden, on 25–26 August 2015, by kind invitation of Ulf Sjöwall and his staff, while Milton Delves of Semacare kindly sponsored some of the sessions.

Several noted speakers took part in this mostly didactic meeting, including Alf Brubakk, Ron Nishi, Neal Pollock, David Doolette, Mikael Gennser, Peter Wilmshurst and Peter Germonpré, with 27 delegates from 12 countries in attendance. The programme included historical, theoretical and hands-on sessions, as well as a much needed consensus discussion on the standardisation of measurement protocols at the end of the second day.

The consensus guidelines for the use of ultrasound for diving research that were developed at the meeting will be published in early 2016. More information, a link to pictures and news of a taught ultrasound course for 2016, to be run in conjunction with the Scott Haldane foundation, can be found on the website:
<http://ultrasound2015.wix.com/ultrasound2015>

Figure 1
Some of the speakers and attendees at the Ultrasound 2015 meeting; from left: Peter Germonpré, Johan Douglas, Alf Brubakk, Lesley Blogg, "JJ" Brandt-Corstius, Ron Nishi, Mikael Gennser, Peter Wilmshurst, David Doolette, Neal Pollock and Andreas Møllerløkken



41st EUBS ASM − Amsterdam 2015

Sailing among the history of hyperbaric medicine

Some historical events remain fixed in our dreams related to particular objects, such as a city. In 1961, Professors Boerema and Brummelkamp reported impressive results in patients with gas gangrene who were operated on in a pressurized surgical theatre at the Wilhelmina Gastuis Hospital. At the first International Conference on Hyperbaric Medicine in 1963, it was agreed that debridements did not need to be done under pressure, but that the high oxygen concentration in the blood was the main reason for their success. Hyperbaric surgery was soon interrupted but the modern developments in hyperbaric medicine continued, linked to the city of Amsterdam as a place that any hyperbaric specialist must visit some time in their lifetime.

Professor Dirk Bakker organized in 1983 the First European Conference on Hyperbaric Medicine. For some young people, as I was at that time, it was a remarkable opportunity to see the original hyperbaric surgical room used by Boerema, although by that time it was out of service. In 1990, Professor Bakker managed to bring together the International Conference on Hyperbaric Medicine (ICHM) and the meetings of the Undersea and Hyperbaric Medical Society (UHMS) and the European Undersea Baromedical Society (EUBS). Really it was not a big Conference but the simultaneous meetings of three different societies each following their own programme was a remarkable achievement.

EUBS members were delighted when another EUBS Meeting was to be held in Amsterdam in 2015. The Academic Medical Centre (AMC) is an impressive institution, with a warm, open design that provides open areas for refreshments or to view interesting exhibitions such as that of medical jewellery made from parts of old medical devices.

On Wednesday morning, an open Workshop was dedicated to the use of heliox in the treatment of decompression sickness (DCS). There was much discussion, without unanimous agreement, but the general conclusion was that this sophisticated hyperbaric therapy, not only based on oxygen but also on the dynamics of the uptake and elimination of inert gases, still has a role in the treatment of DCS.

The Chairmen of the Congress, Drs Albert van der Brink, and Rob van Hulst led the opening ceremony at which an emotive tribute to Professor Boerema was given by some of his relatives, who were introduced by Professor Bakker. There were four main themes to the conference: the basic diving sciences; in-depth research on the basic mechanisms of hyperbaric oxygen (HBO); a wide variety of posters dealing with a miscellany of topics, whilst the keynote lectures were excellent.

A famous Dutch astronaut, André Kuipers described the challenges in the selection process as an astronaut, followed by his six-month experience in the International Space Station. Dick Clark offered a well-documented review on the history of hyperbaric technology and medicine, demonstrating that Boerema was not actually the first to utilise HBO in Europe. Professor Lucas Stalpers presented a lecture entitled "*HBO: the panacea for radiation injury?*" in which he explained that HBO is not, in fact, a panacea for radiation injuries but, rather, a very useful ancillary treatment when correctly applied. We all held our breath whilst listening to Professor Erika Schagatay's lecture on 50 years of study of apnoea and breath-hold diving.

The main programme was surrounded by a variety of other meetings, commissions, boards, satellite events and different activities for those belonging to the European Diving Technology Committee (EDTC), the European Committee for Hyperbaric Medicine (ECHM), the Executive Committee of the EUBS, the Paramedical Association, the Editorial Board of *Diving and Hyperbaric Medicine*, a Divers Alert Network Day, a course for chamber operators and other gatherings, both formal and informal.

I have left to the end the most important part of any conference: networking during coffee and meal breaks and banquets. This is not a joke on my part but, rather, a serious conviction of the importance of this component of any conference. Yes, papers are essential, but many of these will be published later in the medical and scientific literature. During the intervals between sessions one has the opportunity to talk with the presenters, or debate with people with whom one disagrees.

Amsterdam, a city of canals, offered us the best of its museums, concerts, architecture and ambience as well as the coincidental *Sail 2015* exhibition. The canals were filled by hundreds of boats of all types, with amazing crews enjoying their sailing experience. Amsterdam's waterways reminded us of the daily traffic jams in the big cities from whence many of us come. If you don't believe me, go to the next Amsterdam Sail Exhibition in five years. You will be amazed by the strong personality of this old city; pause on the greensward beside the waters and, last but not least, visit the AMC Hospital to see the most famous historical hyperbaric chamber in Europe.

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Key words
Medical society; history; meetings; general interest

Capita Selecta Diving Medicine Academic Medical Centre, University of Amsterdam, The Netherlands

Course calendar 2016

CSD offers advanced courses (content conforms to ECHM-EDTC Level 1, 2D).

19 March: Symposium *Medication and Diving* (ENT, neurology, psychiatry, pulmonology, cardiology, internal medicine, 6 cp); AMC, Amsterdam
24 September–01 October: Mini-congress *Diving Medicine* (5 plenary lectures by Adel Taher, 10 invited lectures, free contributions, 18 cp); Paradise Bay, Malta
November: *Exercise under water and working under pressure* (6 cp); AMC, Amsterdam

For further information: <www.diveresearch.org>

European Committee for Hyperbaric Medicine 10th Consensus Conference

Dates: 15–16April 2016
Venue: Lille, France

The European Committee for Hyperbaric Medicine (ECHM) has in its objectives the continuous improvement in the quality of care and safety in hyperbaric medicine. One of the tools used to achieve this is the organization of consensus conferences to develop guidelines. Nine such conferences have been organized and their recommendations widely promulgated. Two of these, in 1994 and 2004, were especially focused on the organization, indications and quality of care in hyperbaric medicine. Ten years on, it is time to review and update these guidelines based on advances in medical knowledge and the experience gained in clinical practice during that period.

In 1994, the guidelines were developed by a jury from expert reports and discussion with the conference audience. In 2004, these guidelines were improved by grading the recommendations based on the level of evidence for and the clinical importance of each recommendation. In 2016, ECHM wishes to take this a step further by reviewing each recommendation and enhancing the grading system. Recognized experts in each field will produce a report on a topic with an exhaustive literature survey, a synthesis of the evidence and a proposal for revised recommendations. These reports will be circulated amongst the expert group and each will be asked to weight their assessment of the proposed recommendations. During the conference, the reports and expert opinions will be presented to the audience which will have an opportunity to discuss and amend the reports before a final consensus on each recommendation is issued.

For information: <www.echm-lille-consensus-2016.org>

Scott Haldane Foundation

The Scott Haldane Foundation is dedicated to education in diving medicine, organizing 230 courses over the past 20+ years. In 2016 SHF is targeting more and more on an international audience with courses world wide.

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

SHF courses for 2016
19 March: *NEW* Refresher course Diving Accidents; Amsterdam, NL
1–2 April: Basic Course Diving Medicine (level 1 part 1); Zeist, NL
9, 15 and 16 April: Basic Course Diving Medicine (level 1 part 2); Amsterdam, NL
21–28 May: *NEW* In-depth course HBOt and decompression; São Vincente, Cape Verde
4–11 June: *NEW* Basic course Lungs and Diving; Bonaire, Netherlands Caribbean
21–22 September: Basic Course Diving Medicine (level 1 part 1); Al Sifah, Oman
24 Sept–01 October: Basic Course Diving Medicine (level 1) part 2; Al Sifah, Oman
October: *NEW* Refresher course Diving Accidents; NL
5–12 November: Basic Course Diving Medicine (level 1 part 1); tbd
12–19 November: *NEW* 24th In-depth Course Diving Medicine; tbd
19–26 November: *NEW* 24th In-depth Course Diving Medicine; tbd
Tbd: In-depth course "A life-long diving" (level 2); Loosdrecht, NL
Tbd: *NEW* Ultrasound hands-on workshop; Europe

For further information: <www.scotthaldane.org>

Hyperbaric Oxygen, Karolinska

Welcome to: <http://www.hyperbaricoxygen.se/>.
This site, supported by the Karolinska University Hospital, Stockholm, Sweden, offers publications and free, high-quality video lectures from leading authorities and principal investigators in the field of hyperbaric medicine.

You need to register to obtain a password via e-mail. Once registered, watch the lectures online, or download them to your iPhone, iPad or computer for later viewing.

For further information contact:
Folke Lind, MD PhD
E-mail: <folke.lind@karolinska.se>
Website: <www.hyperbaricoxygen.se>

Professor Robert van Hulst

Professor Robert van Hulst gave his inaugural oration entitled "*hyperbaric and diving medicine, therapy under pressure*" on 06 November 2015 to mark his appointment as Professor at the Academical Medical Center (AMC), Amsterdam. This appointment is the result of cooperation between the AMC and the Royal Dutch Navy. Rob remains a reservist with the rank of Captain and is a senior consultant in diving and hyperbaric medicine to the navy.

EUBS and SPUMS congratulate him on receiving this well-deserved academic appointment, as well as best wishes in his new role at AMC.

ANZ Hyperbaric Medicine Group Introductory Course in Diving and Hyperbaric Medicine 2016

Dates: 22 February–04 March
Venue: The Prince of Wales Hospital, Randwick, Sydney
Cost: AUD2,400.00 (inclusive of GST)
Course Conveners: Associate Professor David Smart (Hobart), Dr John Orton (Townsville)

The Course content includes:

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

Approved as a CPD learning project by ANZCA: (knowledge and skills category)
56 hours for attendance at lectures and presentations for one credit per hour
24 hours for workshops/PBLDs/small group discussions for two credits per hour

Contact for information:
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E-mail: <Gabrielle.Janik@sesiahs.health.nsw.gov.au>

Advertising in *Diving and Hyperbaric Medicine*

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

Details of advertising rates and formatting requirements are available on request from:
E-mail: <editorialassist@dhmjournal.com>

Instructions to authors

A downloadable pdf of the 'Instructions to Authors' (revised August 2015) can be found on the *Diving and Hyperbaric Medicine* (DHM) website: <www.dhmjournal.com>. Authors must read and follow these instructions carefully.

All submissions to *DHM* should be made using the portal at <http://www.manuscriptmanager.com/dhm>. Before submitting, authors are advised to view video 5 on how to prepare a submission on the main Manuscript Manager web site <http://www.manscriptmanager.com>.

In case of difficulty, please contact the Editorial Assistant by e-mail at <editorialassist@dhmjournal.com>.

The

SPUMS

website is at
<www.spums.org.au>

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DAN ASIA-PACIFIC DIVE ACCIDENT REPORTING PROJECT

This project is an ongoing investigation seeking to document all types and severities of diving-related accidents. All information is treated confidentially with regard to identifying details when utilised in reports on fatal and nonšfatal cases. Such reports may be used by interested parties to increase diving safety through better awareness of critical factors. Information may be sent (in confidence unless otherwise agreed) to:

DAN Research
Divers Alert Network Asia Pacific
PO Box 384, Ashburton VIC 3147, Australia
Enquiries to: <research@danasiapacific.org>

DAN Asia-Pacific NON-FATAL DIVING INCIDENTS REPORTING (NFDIR)

NFDIR is an ongoing study of diving incidents, formerly known as the Diving Incident Monitoring Study (DIMS). An incident is any error or occurrence which could, or did, reduce the safety margin for a diver on a particular dive. Please report anonymously any incident occurring in your dive party. Most incidents cause no harm but reporting them will give valuable information about which incidents are common and which tend to lead to diver injury. Using this information to alter diver behaviour will make diving safer.

The NFDIR reporting form can be accessed on line at the DAN AP website:
<www.danasiapacific.org/main/accident/nfdir.php>

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Diving and Hyperbaric Medicine Volume 45 No. 4 December 2015

Diving and Hyperbaric Medicine is indexed on MEDLINE, SciSearch® and Embase/Scopus

Printed by Snap Printing, 166 Burwood Road, Hawthorn, Victoria 3122, <hawthorn@snapprinting.com.au>