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HIGHLIGHTED TOPIC | *The Physiology and Pathophysiology of the Hyperbaric and Diving Environments*

Short oxygen prebreathe periods reduce or prevent severe decompression sickness in a 70-kg swine saturation model

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Mahon RT, Dainer HM, Gibellato MG, Soutiere SE. Short oxygen prebreathe periods reduce or prevent severe decompression sickness in a 70-kg swine saturation model. *J Appl Physiol* 106: 1459–1463, 2009. First published January 29, 2009; doi:10.1152/jappphysiol.91058.2008.— Disabled submarine (DISSUB) survivors are expected to achieve saturation with inert gas. However, rescue procedures may not accommodate staged decompression, raising the potential for severe decompression sickness (DCS). Alternatives to standard recompression therapy are needed. It has been demonstrated in humans that isobaric oxygen “prebreathing” (OPB) can accelerate decompression in a DISSUB scenario. In 70 kg swine saturated at 2.82 atm absolute (ATA), 1 h of OPB eliminated death and reduced severe DCS. We hypothesized that even shorter periods (<1 h) of OPB before no-stop decompression from saturation at 2.82 ATA could reduce the incidence of DCS in a large animal model. Catheterized Yorkshire swine (68.8 ± 1.7 kg) in individual Plexiglas boxes within a large animal hyperbaric chamber were compressed to 2.82 ATA for 22 h. Following saturation and while still at depth, breathing gas was switched to >95% O₂ for 45 min (OPB₄₅), 15 min (OPB₁₅), or 5 min (OPB₀₅) of OPB, or no OPB (control). The chamber was then decompressed without stops (0.91 ATA/min). Observers then entered the chamber and recorded signs of DCS for 2 h. All OPB periods significantly reduced the risk of developing type II DCS. OPB₄₅ eliminated severe DCS. Controls had a 2.5 times greater risk of developing type II DCS than OPB₀₅ ($P = 0.016$). OPB₄₅ and OPB₁₅ significantly reduced type I DCS compared with controls. These results support the potential of OPB as an alternative to staged decompression and that OPB could be expected to improve outcome in a DISSUB rescue scenario.

disabled submarine; nonrecompressive therapy; preoxygenation; prebreathe

EXPOSURE to hyperbaric air causes the human body to absorb inert gas. Levels of absorption are based on depth and duration as well tissue perfusion and gas solubility. After remaining at depth for an extended period of time the tissue beds become saturated with inert gas. When a diver’s tissues become saturated with inert gas, further exposure at depth no longer increases the inert gas load (4, 7, 18). Decompression from saturation is generally a lengthy undertaking, with decompression from just 60 feet of sea water (fsw) requiring 14–16 h of staged decompression (22, 29).

In certain situations this lengthy decompression may not be feasible. One such scenario is a disabled submarine (DISSUB). It is possible that the internal pressure of a DISSUB would increase based on partial flooding and the use of emergency air-breathing systems (25). Under such circumstances, it is likely that submariners waiting for the deployment of submarine rescue assets will achieve inert gas saturation. Lengthy decompression onboard a rescue vehicle, with their limited passenger capacity, imperils remaining survivors who are likely facing air contamination, fire, and other hazards. Lengthy decompression is, therefore, unacceptable. Yet, rapid decompression of the rescued carries an increased risk of morbidity and mortality from decompression sickness (DCS).

Probabilistic modeling by Weathersby et al. (35) estimated the risk of DCS in humans rapidly decompressed (no-stop decompression) from saturation at 60 fsw to be ~40%. In a single-factor design study of 70-kg swine performed by our group, the incidence of severe DCS in animals rapidly decompressed from saturation at 60 fsw was 85% (31). Means to mitigate this risk are needed. Since DCS results, in part, from the release of inert gas from tissues as pressure is decreased, the reduction or elimination of inert gas should decrease DCS.

The use of oxygen before a decrease in ambient pressure has been termed “oxygen prebreathe” (OPB). OPB has been well recognized to decrease DCS in high-altitude decompression and is widely used in high-altitude and space extravehicular activity. Webb and Pilmanis (37, 38) demonstrated that 1 h of OPB at 1 atm absolute (ATA) delivered while exercising significantly decreased DCS on rapid ascent to 7,000 m.

In hyperbaric environments, 1 h OPB eliminated severe DCS in 70-kg swine that underwent rapid decompression from saturation at 60 fsw (2.8 ATA) (31). Although these results were promising, the logistic, technical, and safety complications of providing 1 h of oxygen to the submarine or disabled submarine rescue vehicle warrant efforts for even more aggressive oxygen prebreathe profiles. Recently, Dainer and colleagues (12) demonstrated the potential of very short OPB periods when they showed that as little as 10 min OPB decreased DCS from 88% to 41% after rapid ascent from saturation at 132 fsw (5 ATA) in 20-kg swine.

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To determine if shorter OPB times in a 60 fsw rapid decompression model could reduce the incidence of DCS in a human-sized animal model, we saturated nonsedated 70-kg swine at 60 fsw and provided OPB times of less than 1 h before no-stop decompression. We show that all OPB periods significantly reduced type II DCS compared with air controls; 45 min of OPB eliminated severe DCS from hyperbaric saturation dropout. Fifteen and 45 min of OPB resulted in statistically significant reductions of relative risks compared with controls.

The ability of even very short periods of OPB to reduce DCS after saturation dropout from 2.82 ATA supports the potential of OPB as an alternative to staged decompression.

MATERIALS AND METHODS

The methods reported were conducted according to the principles set forth in the *Guide for the Care and Use of Laboratory Animals* (Institute of Laboratory Animal Resources, National Research Council, National Academy Press, 1996). Before commencing, our Institutional Animal Care and Use Committee reviewed and approved all aspects of this protocol. The institutional animal care facility is fully AAALAC accredited, and the veterinary staff is familiar with our 70-kg swine saturation model.

Animals. Forty-nine male Yorkshire swine (68.8 ± 1.7 kg; Biotechnical Industries, Dunsborough, PA) were housed in free-running cages at an animal care facility. Animals were on site for 5 days before any procedures. At the housing facility, food (2–2.5% of body weight twice daily; Lab Diet Mini-Pig Grower, Quality Lab Products, ElkrIDGE, MA) and full access to water were provided.

Surgical preparation. To allow recovery from surgical procedures before hyperbaric exposure, subjects underwent external jugular vein catheter placement on the day before the experiment. Anesthesia induction was performed with ketamine (Ketaject 100 mg/ml; Phoenix Pharmaceutical, St. Joseph, MO; 20 mg/kg) and xylazine (Xylaject 100 mg/ml; Phoenix Pharmaceutical, St. Joseph, MO; 2 mg/kg) intramuscularly. After induction, animals were maintained on Isoflurane inhalant anesthesia (Halocarbon Products, Rover Edge, NJ, 2–5%) via mask. The external jugular vein was catheterized with a 14-gauge, 30-cm single-lumen catheter (Central Venous Catheterization Set; Arrow International, Reading, PA) via the modified Seldinger technique (2). The catheter was advanced to 8–10 cm from the skin incision site, sutured in place, and taped to the skin. Using connector Tygon tubing (Cole-Parmer, Vernon Hills, IL) the catheter was brought through a vest (designed and crafted in house) with an exit site on the dorsal thorax of the swine. Full ambulation after recovery was verified before return to the holding pen, where the animal remained overnight.

On the day of the hyperbaric exposure animals were transported to the hyperbaric lab, and each was placed into a Plexiglas box (30 in. \times 4 in. \times 38 in., manufactured in house) within our Multiple Large Animal Chamber (MLAC). The MLAC is a steel-hulled hyperbaric chamber of 450-cubic ft floodable volume and pressure tested to 1,000 fsw. The Plexiglas boxes allow for animal isolation and independent control of the breathing gas mixture while diminishing restrictions of animal movement. The external jugular vein catheter was connected to a sterile line, fed through Tygon tubing with a swivel top and out of the Plexiglas box. The sterile line then passed through a hull penetrator port of the MLAC and was connected to a high-pressure positive displacement infusion pump (Mini pump; Milton Roy, Ivyland, PA). This system allowed for delivery of medication at depth if there was evidence of unanticipated animal distress, or euthanasia in case of a chamber emergency. Water was available ad libitum via a drinking valve (Hog Nipple; Edstrom Industries, Waterford, WI) that penetrated the Plexiglas box. Food was not provided during hyperbaric exposure.

Hyperbaric exposure. The MLAC was pressurized with air to 60 fsw at a rate of 30 ft/min. Animals were monitored via closed-circuit television for any signs of distress related to middle ear barotraumas (head shaking, nystagmus). To achieve inert gas tissue saturation, animals remained at 60 fsw for 22 h (13). The chamber and Plexiglas box atmospheres were monitored with a Geotech Anagas Dive Air Analyzers (Geotech, Denver CO). Air composition was maintained at 21% (\pm 2%) oxygen and $<0.05\%$ CO₂ surface equivalent. Temperature ($26.6 \pm 1^\circ\text{C}$) and humidity ($50 \pm 5\%$) were controlled via an environmental control system piped to the MLAC.

In the first set of experiments, after 22 h at 60 fsw, paired animals were exposed to one of three groups: OPB of 15 min (OPB₁₅), OPB of 45 min (OPB₄₅), and no OPB (control). Time on oxygen was defined from the time when the fraction of inspired O₂ reached $>95\%$ within the Plexiglas box (\sim 2 min from gas switch). After treatment animals were rapidly decompressed to the surface at a rate of 30 fsw/min. Based on the results of the first series, a third group was later tested and received 5 min OPB (OPB₀₅).

Surface observation. On decompression to surface pressure (1 ATA), the MLAC chamber door was opened and an observer for each animal entered the chamber. Observers fit animals, which remained in their Plexiglas boxes, with a tail pulse oximeter (VetOx 4404; Heska, Loveland, CO). Heart rate and oxygen saturation were recorded every 5 min as well as any signs of cutis marmorata or animal distress. After the initial 2-h observation period the Plexiglas boxes were opened and the animals walked out of the MLAC. A neurological exam consisting of observation for nystagmus, and examinations of gait, limb strength, and tactile sensibility (pin prick) were then performed. The animals were moved back to the housing facility, placed into the free-running cages, and examined every 24 h for an additional 6 days. After this observation period the animals were killed (1 ml/kg Euthosol iv; Verbac AM, Ft. Worth, TX).

DCS definitions. DCS is generally divided into two broad categories. Type I DCS includes 1) cutis marmorata, a skin manifestation that appears as a hyperemia that progresses to dark, violet patches; and 2) pain only. Type II DCS includes evidence of focal neurological deficits or cardiopulmonary compromise.

Cutis marmorata, commonly known as “skin bends,” is easily recognized by its typical violaceous appearance (9), while pain-only DCS was inferred from signs that included limb lifting or foot curling along with vocalization. Signs of type I DCS were recorded to the nearest minute. If the subject appeared to be in pain, Ketorlac (1 mg/kg iv, single dose, Baxter Health Care, Deerfield, IL) was administered via the existing central line. Type II DCS, the more severe and life-threatening form of DCS, is of two varieties, neurological and cardiopulmonary. For the purposes of this study, neurological DCS was defined as motor deficit (limb weakness, repeated inability to stand after being righted by the investigator), paralysis (limb flaccidity, hypotonia), or sensory deficit. With small modifications to Dromsky et al. (14), cardiopulmonary DCS was defined as sustained (\geq 1 min) clinical evidence of severely compromised oxygenation and hemodynamic instability, specifically any of the following: hemoglobin saturation $< 80\%$, mean heart rate $\geq 150\%$ of baseline, and mean respiratory rate $\geq 200\%$ baseline. Animals diagnosed with cardiopulmonary DCS were immediately euthanized (1 ml/kg Euthosol iv; Verbac AM) via central line.

Statistics. Development of DCS in its various forms was displayed using the empirical Kaplan-Meier method for each treatment group. Log-rank tests were performed for group effect on development of DCS. Pair-wise Cox proportional hazards regression models between groups were run assuming right censoring for animals not experiencing DCS within the 2 h observation after surfacing. Pairwise Cox proportional hazards models were run with weight and/or change in weight during the dive as covariates in addition to the group indicator variable. As none of the models indicated a role for weight in the analysis, the final models simply included group as the only independent variable. The 95% confidence intervals for the hazard ratios

(estimates of relative risks) of DCS were obtained. Data regarding the development of neurological and cardiopulmonary forms of DCS were analyzed using simple Fisher's exact tests on the two \times two tables for DCS development vs. oxygen prebreathe or control group. The mean weights before the dives and the mean weight changes during the dives were calculated for each group and compared using an ANOVA procedure. An α -level of 0.05 was used in all analyses. S-plus 2000 software functions were employed for all analyses.

RESULTS

The mean weights and mean changes in weight during the dive for each group are presented in Table 1. The *F*-statistic for the ANOVA in each case corresponded to *P* values of 0.19 and 0.87, respectively, which indicate no difference between groups.

Type II DCS. Kaplan-Meier curves for the survival times until developing type II DCS are plotted in Fig. 1. Outcome data for all experimental groups are presented in Table 1. All three periods of OPB administered before rapid decompression from hyperbaric saturation at 60 fsw significantly reduced the overall incidence of cardiopulmonary DCS to 8.8% (3/34) of OPB subjects from 73.3% (11/15) in controls (Fisher's exact test on pooled OPB data vs. control; $P < 0.001$). The log-rank test achieved statistical significance with an estimated relative risk of developing type II DCS in the control group of 4.0 times that of the combined OPB group [95% confidence interval (CI) = (2.11, 7.58), $P < 0.001$]. OPB₄₅ eliminated severe DCS. Pairwise Cox proportional hazards models were run for the control group and the OPB₀₅ and OPB₁₅ groups with respect to development of cardiopulmonary DCS. The relative risk for the development of cardiopulmonary DCS for the control group vs. the OPB₀₅ group was 2.53 [95% CI = (1.19, 5.38), $P = .016$], and for the control group vs. the OPB₁₅ group was 4.17 [95% CI = (1.49, 11.70), $P = 0.007$]. In other words, at any time interval during the post-surface observation period there were likely to be 2.53 times more cases of cardiopulmonary DCS in control animals than there were cases of cardiopulmonary DCS in animals that received just 5 min of OPB and more than 4 times more cases than subjects receiving 15 min of OPB. With only two animals from the OPB₀₅ and one animal from the OPB₁₅ groups developing signs of cardiopulmonary DCS, relative risk between the OPB₀₅ and OPB₁₅ could not be statistically distinguished. Comparisons including the OPB₄₅ group were not performed as no type II DCS occurred in this group.

Neurological DCS was also significantly reduced by OPB (Fisher's exact test; $P < 0.001$). Of note, the only animal in the OPB groups diagnosed with neurological DCS also developed

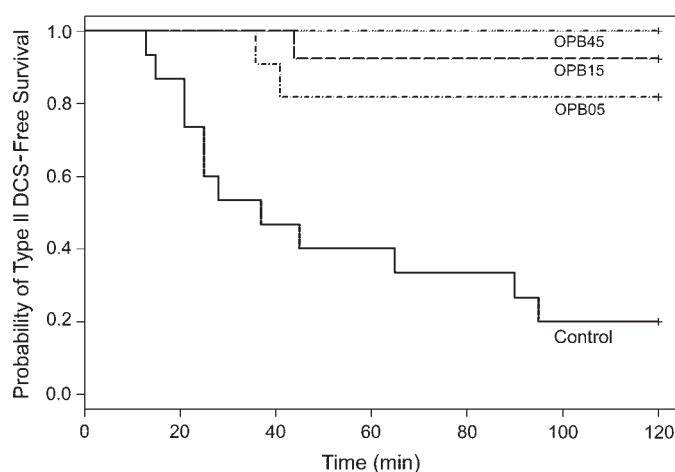


Fig. 1. Kaplan-Meier curves for the probability of type II decompression sickness (DCS)-free survival vs. time. Manifestations of type II DCS were recorded during a 2-h observation period after surfacing for the 3 oxygen prebreathe (OPB) treatment groups and their controls in 70-kg swine saturated at 2.82 atm absolute (ATA). OPB₄₅, OPB₁₅, and OPB₀₅ refer to OPB of 45, 15, or 5 min, respectively; control, no OPB.

cardiopulmonary DCS. Neurological DCS was identified in 40% of controls.

Type I DCS. The Kaplan-Meier curves of type I DCS-free survival during the 2-h post-surfacing observation period are plotted in Fig. 2. A log-rank test for differences in survival curves resulted in a chi-squared statistic of 18.2 with 3 degrees of freedom, indicating a statistically significant difference in type I DCS-free survival between groups ($P < 0.001$). Only 1 of 10 animals in the OPB₄₅ group developed type I DCS during the 2-h observation period compared with 13 of 15 (87%) in controls. Results of the pairwise Cox proportional hazard model analysis are shown in Table 2. The control group animals exposed to air only were 2.12 times more likely to develop type I DCS than those in the OPB₁₅ group ($P = 0.005$) and 4.15 times more likely than the OPB₄₅ group ($P = 0.006$). Alternatively, when expressed in the reciprocal, OPB₁₅ and OPB₄₅ group reduced the relative risk to 46% and 24% of the controls, respectively. Note that the difference in relative risk between the OPB₄₅ and OPB₀₅ groups approached ($P = 0.062$) the established level of statistical significance. There was no detectable risk reduction between the OPB₀₅ and control groups for development of type I DCS.

No animals developed pain only type I DCS during the chamber observation. Two animals (1 OPB₄₅ and 1 OPB₀₅)

Table 1. Weight characteristics and DCS outcomes in control and OPB groups

Group	<i>n</i>	mwt	SE _{mwt}	mΔ(wt)	SE _{mΔ(wt)}	Type I DCS: DCS _{cutis}	Type II DCS	
							DCS _{neuro}	DCS _{cardiopulm}
Control	15	69.5	0.83	-1.64	0.28	13	6	11
OPB ₀₅	11	69.7	0.81	-2.50	0.59	6	0	2
OPB ₁₅	13	68.8	0.77	-1.33	0.17	6	1	1
OPB ₄₅	10	67.4	0.55	-1.20	0.42	1	0	0

Characteristics for the control, oxygen prebreathe (OPB) of 5 min (OPB₀₅), OPB of 15 min (OPB₁₅), and OPB of 45 min (OPB₄₅) groups: mwt, mean weight; SE_{mwt}, standard error of the mean weight; mΔ(wt), mean change in weight during dive; SE_{mΔ(wt)}, standard error of the mean change in weight; DCS_{cutis}, no. of subjects with cutis decompression sickness (DCS); DCS_{neuro}, no. of subjects with neurological DCS; DCS_{cardiopulm}, no. of subjects with cardiopulmonary DCS.

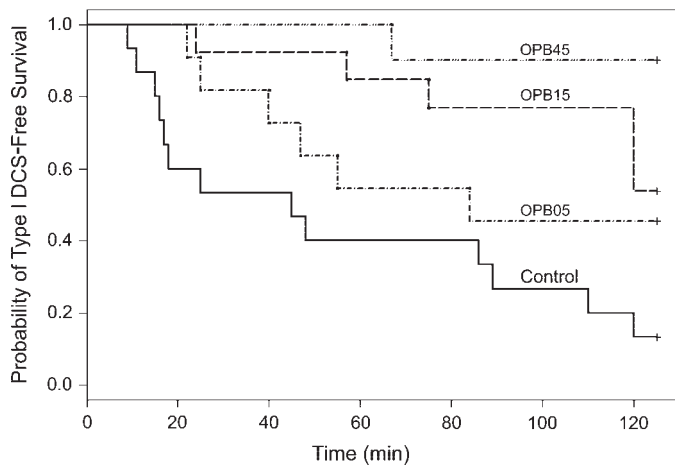


Fig. 2. Kaplan-Meier curves for the probability of type I DCS-free survival vs. time. Manifestations of type I DCS were recorded during a 2-h observation period after surfacing for 3 OPB treatment periods and their controls in 70-kg swine saturated at 2.82 ATA.

developed pain attributed to DCS in the subsequent 24 h after return to their pens.

DISCUSSION

This study shows that as little as 5 min of OPB significantly decreases the risk of type II DCS, with OPB of 45 min being fully protective against type II DCS (Fig. 1) in our model of drop-out decompression from 2.8 ATA in saturated 70-kg swine. We also show that OPB of 15 or 45 min significantly reduces the relative risk for type I DCS (Table 2).

Although there is no definitive etiology for DCS, bubble formation from inert gas exiting body tissues following decompression is thought to initiate a cascade of events leading to clinical manifestations that can range from mild joint pain to death (19, 30). Inert gas is responsible for the formation of microbubbles that eventually coalesce and affect oxygen delivery to tissue beds (8, 17). Decompression is also associated with inflammatory and coagulation pathway activation (21, 32, 34). The combination of altered tissue perfusion, and inflammatory and coagulation alterations, likely causes the clinical syndrome of DCS.

When environments are well controlled, decompression follows established schedules that allow the time needed to off-gas slowly and minimize bubble formation (7, 23, 29). This is achieved either by controlled ascent or by recompression in a hyperbaric chamber immediately on surfacing. In emergency situations, the ability to properly execute optimally timed air decompression is compromised. One method to decrease decompression time is by using hyperbaric oxygen (HBO).

The use of hyperbaric oxygen (HBO) accelerates inert gas elimination and is well established in the prevention and treatment of DCS (5, 24). By eliminating N_2 from the inhaled gas mixture, O_2 breathing maximizes the difference between the partial pressure of N_2 in the tissues and the partial pressure of N_2 in the capillaries. This maximizes the diffusion gradient for N_2 and, thus, the elimination of accumulated inert gas, which is the primary concern in decompression schedules.

Unfortunately, nitrogen elimination using HBO has not been closely examined in swine. At surface pressures, use of 1 ATA

O_2 results in ~25% of total body nitrogen being eliminated in sedated swine during a 20-min period (26). Results from resting humans suggests that ~20% of total body nitrogen may be eliminated with oxygen at 1 ATA in the first 15 min (6), and ~25% at 2 ATA (10, 11). There is likely a critical volume of inert gas release necessary to induce DCS (20). In our swine model it is quite possible that the amount of nitrogen eliminated with OPB was adequate to decrease the incidence of DCS. Previous research has shown that a reduction in inert gas load by ~5% reduced any DCS risk by ~50% (16), a value similar to what we find with 5 min OPB.

Aside from inert gas elimination, HBO appears to have other effects that may decrease the DCS risk. HBO reduces gas nuclei that theoretically serve as the basis for bubble formation (1), decreases leukocyte adhesion by a β_2 -integrin-dependent mechanism (27), and rapidly increases nitric oxide formation (33).

Interestingly, Thom et al. (33) demonstrated the ability of 2.8 ATA oxygen to maximally increase perivascular NO levels within 10 min. As the origin of gas nuclei may arise at the blood-endothelial interface, NO may itself decrease bubble formation by changes in the endothelial surface. This finding is even more intriguing given the recent findings concerning decreased bubble formation and DCS with NO donors (28). Wisloff et al. (39) demonstrated less DCS in a rat model when a NO donor was used and that timed pre-dive exercise reduced DCS risk. Also, a NO donor has recently been demonstrated to decrease bubble formation in human divers when administered before diving (15). Similarly, inhibition of NO synthase activity in a separate study increased death of rats from DCS (40). Complicating these apparent benefits is evidence that NO increases the risk of oxygen toxicity (13).

Although pharmacological-like benefits of OPB are intriguing, studying the potential mechanisms of OPB was beyond the scope of the present study. This limitation to the presented work should incite further research as the toxicity of oxygen itself may limit its utility at high pressure. Exploration of the potential role of OPB with respect to NO generation, leukocyte adhesion, and quantification of inert gas elimination are certainly warranted and may further improve diver safety.

The primary strength of this study is the use of the non-sedated, nonconstrained 70-kg swine. This model allows for endpoints that are not subject to the criticisms related to sedation or anesthesia. It is recognized that many anesthetic agents may impact cardiovascular and respiratory status that would in turn impact DCS risk. Furthermore, as DCS risk is strongly related to species weight (3, 35, 36), results from

Table 2. Relative risk of developing type I DCS between control and OPB groups

Model	RR	95% CI	P Value
Control vs. OPB ₀₅	1.50	(0.93, 2.43)	0.100
Control vs. OPB ₁₅	2.12	(1.25, 3.58)	0.005
Control vs. OPB ₄₅	4.15	(1.49, 11.1)	0.006
OPB ₀₅ vs. OPB ₁₅	1.25	(0.71, 2.22)	0.440
OPB ₀₅ vs. OPB ₄₅	2.75	(0.95, 7.69)	0.062
OPB ₁₅ vs. OPB ₄₅	2.33	(0.81, 6.67)	0.120

Cox proportional hazards model results: estimated relative risk (RR) of developing type I DCS between OPB groups with associated 95% confidence intervals (CI) and P values.

70-kg swine are likely to be useful in estimating outcomes in humans.

These results may be useful in predicting risk and benefit analyses if humans need to undergo a drop-out decompression from saturation conditions. Such scenarios could be faced in a DISSUB or the commercial diving industry.

In conclusion, as little as 5 min OPB is protective against cardiopulmonary DCS in the saturated 70-kg swine undergoing rapid decompression from 60 fsw. As little as 15 min OPB prevents type I DCS in the same animal model. Even short periods of OPB are reasonable to consider when rapid decompression from 60 fsw is necessary. The mechanisms of this benefit need further exploration.

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