Propranolol Effects on Decompression Sickness in a Simulated DISSUB Rescue in Swine

Angela S. Forbes; David. P. Regis; Aaron A. Hall; Richard T. Mahon; William A. Cronin

INTRODUCTION: Disabled submarine (DISSUB) survivors may face elevated CO_2 levels and inert gas saturation, putting them at risk for CO_2 toxicity and decompression sickness (DCS). Propranolol was shown to reduce CO_2 production in an experimental DISSUB model in humans but its effects on DCS in a DISSUB rescue scenario are unknown. A 100% oxygen prebreathe (OPB) reduces DCS incidence and severity and is incorporated into some DISSUB rescue protocols. We used a swine model of DISSUB rescue to study the effect of propranolol on DCS incidence and mortality with and without an OPB.

METHODS: In Experiment 1, male Yorkshire Swine (70 kg) were pressurized to 2.8 ATA for 22 h. Propranolol 1.0 mg · kg^{-1} (IV) was administered at 21.25 h. At 22 h, the animal was rapidly decompressed and observed for DCS type, onset time, and mortality. Experimental animals ($N = 21$; 69 ± 4.1 kg), $PROP_{1.0}$, were compared to $PROP_{1.0}$-OPB_{45} ($N = 8$; 69 ± 2.8 kg) with the same dive profile, except for a 45 min OPB prior to decompression. In Experiment 2, the same methodology was used with the following changes: swine pressurized to 2.8 ATA for 28 h; experimental group ($N = 25$; 67 ± 3.3 kg), $PROP_{0.5\ bis}$, propranolol 0.5 mg · kg^{-1} bis (twice) (IV) was administered at 22 h and 26 h. Control animals ($N = 25$; 67 ± 3.9 kg) received normal saline.

RESULTS: OPB reduced mortality in $PROP_{1.0}$-OBP_{45} compared to $PROP_{1.0}$ (0% vs. 71%). $PROP_{0.5}$ bis had increased mortality compared to CONTROL (60-% vs. 4%).

DISCUSSION: Administration of beta blockers prior to saturation decompression appears to increase DCS and worsen mortality in a swine model; however, their effects in bounce diving remain unknown.

Forbes AS, Regis DP, HallAA, Mahon RT, Cronin WA. *Propranolol effects on decompression sickness in a simulated DISSUB rescue in swine.* Aerosp Med Hum Perform. 2017; 88(4):385–391.

Time is crucial when rescuing survivors from a disabled submarine (DISSUB). While awaiting rescue the stranded crew may experience decreased temperatures, diminished oxygen, and increased CO_2 levels. The delivery of rescue assets depends heavily on the DISSUB depth, geographic location and sea state, as well as other unpredictable variables; every delay escalates the deteriorating conditions. Currently, CO_2 scrubbing capabilities on a DISSUB can maintain acceptable CO_2 levels for up to 7 d before toxic conditions are reached ($\geq$ 6% CO_2).[22] These risks are then potentially compounded by increased ambient pressures from flooding, pressurized gas bank leaks, or a hull breach.[12] Survivors will achieve inert gas saturation with extended time at increased pressures and require a prolonged staged decompression to minimize decompression sickness (DCS) upon return to surface.[25] Under these circumstances, any prolonged decompression would likely be prohibitive during rescue operations. Alternative methods and techniques to manage such scenarios are imperative.

Executing a safe extraction for trapped submarine crew presents significant logistical challenges. Current submarine rescue assets from the U.S. Navy can be mobilized within 24 h of a DISSUB notification and, depending on location, positioned for submarine rescue to commence within 72 h. Rescue capabilities such as a transfer under pressure (TUP) may become delayed in mobilization to a mass casualty event, unable to deploy rescue assets, or be rapidly overwhelmed. Successful rescue of a full complement of survivors (155

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This manuscript was received for review in July 2016. It was accepted for publication in January 2017.

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DOI: https://doi.org/10.3357/AMHP.4718.2017

personnel) will take more than 100 h (~4 d).[27] When considering the complete timeline for executing rescue operations, it is likely that CO_2 levels will become dangerously high.

Propranolol is a nonselective beta adrenergic antagonist that competitively blocks $beta_1$ and $beta_2$ adrenergic receptors, resulting in decreased heart rate, myocardial contractility, blood pressure, and myocardial oxygen demand. Originally prescribed as an antihypertensive therapy, it is now indicated for the treatment of arrhythmia, ventricular tachycardia, essential tremor, and prophylaxis for myocardial infarction and migraine headaches.[20] With regards to a DISSUB, propranolol was recently recommended to slow the metabolic demands of the crew, resulting in reduced CO_2 production. Reini et al. proposed that an oral dose of propranolol 40 mg every 12 h to DISSUB survivors would lengthen the time to CO_2 toxicity by an additional 11 h.[22]

While propranolol offers the potential to extend a viable DISSUB atmosphere, its impact on DCS is not known and to date no studies have explored the impact of any drugs in this class on DCS. Isoproterenol, a beta agonist, was suggested as an adjuvant to treat cases of refractory hypotension in DCS[7] and thought to possibly decrease DCS incidence because it increases nitrogen elimination.[15] However, Nelson et al. demonstrated that isoproterenol accelerates DCS onset and death in a 20 kg swine mode.[19] Due to the deleterious effects from a beta agonist in the setting of DCS, it is possible that an adrenergic antagonist would beneficially modulate sympathetic tone and diminish oxygen demands of the myocardium. In addition, an isobaric oxygen "pre-breathing" (OPB) in which oxygen is administered before a decrease in ambient pressure demonstrated a reduction in DCS severity in both swine and goats.[4,17] Follow on studies in human trials led to the U.S. Navy recommending a 2-h OPB for DISSUB survivors with an equivalent air depth of 1.8–2.8 ATA.[28] The effect of an adrenergic antagonist, such as propranolol, on tissue perfusion could negatively impact the effects of OPB, requiring a longer duration to achieve equivalent reductions in DCS incidence and severity. Therefore, it is imperative to assess the impact of propranolol on current DISSUB procedures before recommending its use to extend atmospheric viability in a downed submarine.

We used a 70-kg swine model of a dropout decompression from a 2.8 ATA saturation dive to study the effects of propranolol on DCS incidence and mortality. The study was divided into two experiments with the following objectives:

Experiment 1: To evaluate the effects of propranolol (1.0 mg · kg^{-1} IV) on DCS incidence with and without an oxygen prebreathe (OPB) and subsequent dropout from a 2.8 ATA saturation dive.

Experiment 2: To evaluate the effects of a repeated dose of propranolol [0.5 mg · kg^{-1} bis (twice) IV] on DCS incidence and mortality after dropout from a 2.8 ATA saturation dive. It was our hypothesis that propranolol would have no effect on DCS outcomes, supporting its use to prolong a viable DISSUB atmosphere prior to extraction.

METHODS

Animals

The methods reported were conducted according to the principles set forth in the *Guide for the Care and Use of Laboratory Animals*.[18] Before initiating the experiment our Institutional Animal Care and Use Committee reviewed and approved this protocol. The institutional animal care facility is AAALAC accredited, and the veterinary staff is familiar with our 70-kg swine saturation model.

Male Yorkshire Swine (*sus scrofa*, $N = 79$, 68.0 kg $\pm$ 3.7 kg; Thomas Morris, Reisterstown, MD) were examined by a veterinarian upon delivery then acclimatized in free running cages at the animal care facility for 5 d prior to any procedures. Animals were provided a 12-h light/dark cycle, water ad libitum, and twice daily feedings (2–2.5% body weight; Lab Diet Pig Grower, ASAP Animal Specialties and Provisions, Elkridge, MD).

To allow recovery from surgical procedures before hyperbaric exposure, animals underwent external jugular vein catheter placement 24 h prior to the experiment. Anesthesia induction was performed with ketamine (20 mg · kg^{-1}; Ketathesia USP Injection 100 mg · ml^{-1}; Henry Schein Animal Health, Dublin, OH) and xylazine (2 mg · kg^{-1}; Anased Injection 100 mg · ml^{-1}; Lloyd Shenandoah, IA) intramuscularly. After induction, animals were endotracheally intubated and maintained on isoflurane inhalant anesthesia (1–3%; Halocarbon Products, River Edge, NJ). 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. The catheter was advanced to 8–10 cm from the incision site, sutured in place, and taped to the skin. Using a connector Tygon tubing (Cole-Parmer, Vernon Hills, IL) the catheter was brought through a vest (designed and manufactured 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 recovered for an additional 24 h.

On the day of the study, the animals were weighed and transported to the dive chamber. EKG leads were placed on the skin, secured under the cloth vest, and passed through the umbilical with the jugular vein catheter. Individual animals were then placed into a Plexiglas box (30 in × 42 in × 38 in, manufactured in-house) within a Multiple Large Animal Chamber (MLAC), which is a steel-hulled hyperbaric chamber [450-ft^3 floodable volume and pressure tested to 1230 ft of seawater (fsw) equivalent] (Bethlehem Steel Corp, Bethlehem PA). To deliver medication at depth, the external jugular vein catheter was connected to a sterile line, fed through Tygon tubing with a swivel top, passed out of the Plexiglas box, and finally passed through a hull penetrator port of the MLAC. To allow for continuous telemetry, leads from the EKG were similarly bundled in an umbilical with the catheter. A high-pressure positive displacement infusion pump (High Pressure Pump, FMI, Cole Parmer, Vernon Hills, IL) was placed in-line with catheter tubing to allow for infusion of propranolol or normal saline. 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 the hyperbaric exposure. Closed circuit cameras were positioned outside the chamber observation ports and allowed for continuous observation of the animals.

Prior to the hyperbaric propranolol-DCS studies, an analysis for dose vs. heart rate was conducted in the swine. As described above, animals were placed in the MLAC; however, the chamber remained at sea level (unpressurized; 1 ATA). An EKG was collected for 30 min prior to drug infusion, during infusion, and 4 h post infusion. Propranolol was administered at one of three doses: 0.5 mg · kg^{-1}, 1.0 mg · kg^{-1}, or 1.5 mg · kg^{-1} (USP Medisca Product No. 0183-04, Plattsburgh, NY, USP grade $t_{1/2}$ 3-4 h) over 10 min via an infusion pump and the animals were monitored for 4 h post infusion ($N = 2$ per group). The goal was to achieve a decrease from baseline heart rate of 10% to align with the dose response reported in previous work with humans.[22]

For experimental animals, the MLAC was pressurized with air to 2.8 ATA at 30 fsw · min^{-1} (1.9 ATA · min^{-1}) and maintained at 2.8 ATA for 22 h or 28 h, depending on the dive profile. Animals were monitored for any signs of distress or middle ear barotrauma during descent. If distress or barotrauma was observed while traveling, the chamber driver initiated a hold, waited for signs of distress to resolve, and continued travel at a reduced rate. Air composition of the chamber and Plexiglas boxes was monitored with a Gas Analyzer (Alpha Mega 9600, Lincoln, RI). Air composition was maintained at 21% (± 2%) oxygen and < 0.05% CO_2 surface equivalent. Temperature (75–79°F) and humidity (60–70%) were controlled via an environmental control system. Decompression was achieved at the standard rate of 30 fsw · min^{-1}.

To evaluate the effect of propranolol (with or without an OPB) on DCS after dropout from a saturation dive the following groups were used:

Experiment 1
- Propranolol (2.8 ATA for 22 h and propranolol 1.0 mg · kg^{-1}): $PROP_{1.0}$ ($N = 21$)
- Propranolol and OPB (2.8 ATA for 22 h, propranolol 1.0 mg · kg^{-1}, and 45 min OPB): $PROP_{1.0}$-OBP_{45} ($N = 8$)

Experiment 2
- Control (2.8 ATA for 28 h and normal saline): CONTROL ($N = 25$)
- Propranolol (2.8 ATA for 28 h and propranolol 0.5 mg · kg^{-1} bis (twice): $PROP_{0.5bis}$ ($N = 25$)

Experiment 1. Propranolol alone, $PROP_{1.0}$, was compared to propranolol with an OPB, $PROP_{1.0}$-OBP_{45} in a nonrandomized study with compression to 2.8 ATA for 22 h. For $PROP_{1.0}$, propranolol 1.0 mg · kg^{-1} IV, was administered via infusion pump (10 min ± 2 min) after 21 h and 15 min at 2.8 ATA. At 22 h, the animal was decompressed to the surface at a rate of 30 fsw · min^{-1} and observed for 2 h. $PROP_{1.0}$-OBP_{45} underwent the same dive profile and propranolol dosing schedule, except at the end of the 22 h exposure animals received a 45 min OPB at depth prior to decompression. Time on oxygen was defined as the time when the fraction of inspired O_2 reached > 95% (~2 min from gas switch).

Experiment 2. This study used a randomized control design where control animals received equal volumes of normal saline. The methods were the same as Experiment 1, with the following changes: animals were randomized to receive propranolol or equivalent volume of normal saline and pressurized to 2.8 ATA for 28 h. Propranolol 0.5 mg · kg^{-1} bis (IV) or normal saline (IV) was administered in two separate doses, at 22 h and 26 h into the saturation dive; thus, propranolol treated animals received a total dose of 1 mg · kg^{-1}.

Upon reaching the surface (T = 0) the MLAC chamber door was opened and heart rate, respiratory rate, temperature, and arterial oxygen saturation were recorded every 5 min and every 1 min upon signs of DCS. Time of onset was recorded for *cutis marmorata*, cardiopulmonary DCS, neurologic DCS, and death. *Cutis marmorata* is classified as Type I DCS, whereas cardiopulmonary and neurologic DCS are categorized as Type II DCS. *Cutis marmorata* is a cutaneous morbilliform rash. Cardiopulmonary DCS is determined by compromised oxygenation or hemodynamic instability evidenced by a hemoglobin saturation < 80%, mean heart rate > 150% of baseline, and/or mean respiratory rate > 200% of baseline with open mouthed breathing, labored breathing, cyanosis, and/or frothy sputum. Neurologic DCS is indicated with hypotonic paralysis, or repeated inability to stand after being righted by the investigator. Animals that did not survive the 2 h observation were administered euthasol (1 ml/kg Euthasol IV; Verbac AM, Ft. Worth, TX) to ensure death.

After the initial 2 h observation the Plexiglas boxes were opened and the animals removed from the MLAC. The animals were returned to the housing facility, placed into the free-running cages with food and water, re-examined after 24 h, and euthanized.

Statistical Analysis

Statistical analysis was performed using statistical software (Graphpad Prism, Version 6.0, La Jolla, CA). The mean weights before the dives were calculated for each group and compared using a one-way ANOVA. The average heart rate between groups over time was compared using a two-way repeated measures ANOVA. The DCS incidence in each of the groups was analyzed using a Fisher's exact test. A Kaplan-Meir analysis with a log rank test was employed to compare the time to development of DCS between treatment groups. Significance was assigned for a $P \leq 0.5$ for all analyses. A two-tailed test was used for the Fisher's exact test.

Group size for Experiment 1 was based on a prospective pilot study design. There were 25 animals assigned to $PROP_{1.0}$ and 10 animals assigned to $PROP_{1.0}$-OPB_{45} based on previously published DCS outcomes in a swine saturation model.[17] Conversely, a power analysis was conducted for Experiment 2 based on the variance in DCS outcomes observed in Experiment 1. Namely, with an expected 80% incidence of Type II DCS in the

propranolol groups, 50 animals per group adequately powered (80%) the study to detect a 20% absolute decrease in Type II DCS and a significance level of 0.05. An interim analysis was planned and performed at $N = 25$ and based on these results the study was terminated after the interim analysis.

RESULTS

The mean weights were not different among groups at baseline (**Table I**; one way ANOVA, $P = 0.30$, $F = 1.2$, $R^2 = 0.047$). Based on the study design animals were excluded from the analysis if they did not complete the protocol. This included four animals from $PROP_{1.0}$ and two animals from the $PROP_{1.0}$-OPB_{45} that were not included because the jugular venous catheters failed and propranolol was not administered.

Heart Rate

During the dose response study, IV propranolol 0.5 mg · kg^{-1} was associated with a 7% decrease in heart rate; 1.0 mg · kg^{-1}, a 12% decrease; and 1.5 mg · kg^{-1}, a 15% decrease. Additionally, it was determined that it took 30 min for propranolol to reach its max heart rate effect and that the max effect lasted for 3 h. When propranolol was administered at 1.0 mg · kg^{-1} IV and swine were exposed to 2.8 ATA, the mean heart rate decreased from surface baseline (108 bpm) to bottom (75 bpm) to return to surface (91 bpm) (**Fig. 1A**). When propranolol was administered with a repeated dose at 0.5 mg · kg^{-1} bis IV and compared to control, continuous cardiac monitoring revealed a change in mean heart rate from surface baseline (111 bpm vs. 114 bpm) to bottom (70 bpm vs. 80 bpm) to return to surface (81 bpm vs. 91 bpm) in $PROP_{0.5bis}$ and CONTROL, respectively. Propranolol infusion decreased heart rate compared to Control (two-way repeated measures ANOVA, $P = 0.0066$, $F = 8.27$; interaction between treatment and time was significant, $P = 0.0224$, $F = 2.00$), therefore a Bonferroni post test was conducted on only the timepoints after treatment infusion, which also demonstrated a significant difference ($P > 0.05$, $t = 3.173$) (**Fig. 1B**).

Experiment 1, Oxygen Pre-Breath and Propranolol

Propranolol with an OPB decreased incidence of all DCS and mortality. For $PROP_{1.0}$ there was a 100% incidence of Type I DCS, 57% incidence of neurologic DCS, 81% incidence of cardiopulmonary DCS, and 71% mortality. For $PROP_{1.0}$-OPB_{45} there was a 38% incidence of Type I DCS, 13% incidence of neurologic DCS, 0% incidence of cardiopulmonary DCS, and 0% mortality ($P \leq 0.05$ Fisher exact test) (Table I, Exp. 1). $PROP_{1.0}$ decreased survival as compared to $PROP_{1.0}$-OPB_{45} ($P = 0.0022$, log-rank test) with a hazard ratio of 5.22 (95% confidence interval (CI) = 1.81, 15.02). The time at which half of the $PROP_{1.0}$ animals died was 79 min (**Fig. 2A**).

$PROP_{1.0}$ also decreased Type I and II DCS free survival as compared to $PROP_{1.0}$-OPB_{45} ($P = 0.0001$ and $P = 0.0005$, log-rank test) with a hazards ratio of 9.08 (95% CI = 3.59, 22.92) for Type I DCS and a hazards ratio of 5.36 (95% CI = 2.09, 13.78) for Type II DCS. The time at which half of the $PROP_{1.0}$ experienced Type I DCS was 22 min and for Type II DCS was 48 min (**Fig. 3**).

The animal that experienced neurologic DCS in $PROP_{1.0}$-OPB_{45} was diagnosed with paralysis that presented after reaching the surface. This animal did not seize or demonstrate other symptoms for CNS O_2 toxicity.

Experiment 2, Propranolol Alone

The incidence of DCS and mortality was greater in $PROP_{0.5bis}$ as compared to CONTROL. For CONTROL there was 52% Type I DCS, 4% neurologic DCS, 24% cardiopulmonary DCS, and 4% mortality. For $PROP_{0.5bis}$ there was 92% Type I DCS, 44% neurologic DCS, 68% cardiopulmonary DCS, and 60% mortality (Fisher's exact test, $P \leq 0.05$) (Table I, Exp. 2). $PROP_{0.5bis}$ decreased survival as compared to CONTROL ($P < 0.0001$, Log Rank Test) with a hazard ratio of 8.40 (95% CI = 3.08, 22.93). The time at which half of the $PROP_{0.5bis}$ animals died was 116 min (**Fig. 2B**). $PROP_{0.5bis}$ decreased Type I and II DCS free survival as compared to CONTROL ($P = 0.0003$ and $P = 0.0002$, log-rank test) with a hazards ratio of 3.73 (95% CI = 1.82, 7.65) for Type I DCS and a hazards ratio of 4.28 (95% CI = 1.88, 9.79) for Type II DCS. The time at which half of the $PROP_{0.5bis}$ animals experienced Type I DCS was 35 min and Type II DCS was 49 min. The time at which half of the CONTROL animals experienced Type I DCS was 120 min (Fig. 3).

DISCUSSION

To our knowledge, this is the first study to examine the effects of beta antagonism with propranolol on DCS and mortality outcomes in a large animal model. The main finding in our DISSUB rescue model is that propranolol increases Type I and II DCS

Table I. Weight Characteristics and DCS Outcomes in Propranolol, Propranolol + OPB, and Control Groups.

					TYPE II DCS	
EXP	GROUP	*N*	MEAN WEIGHT (SD)	TYPE I DCS	DCS_{Neuro}	DCS_{Cardio}
1	$PROP_{1.0}$	21	69.08 (4.1)	21 (100%)*	12 (57%)*	17 (81%)*
	$PROP_{1.0}$–OPB_{45}	8	68.69 (2.8)	3 (38%)*	1 (13%)*	0 (0%)*
2	CONTROL	25	67.27 (3.9)	13 (52%)*	1 (4%)*	6 (24%)*
	$PROP_{0.5bis}$	25	67.35 (3.3)	23 (92%)*	11 (44%)*	17 (68%)*

Characteristics for Experiment 1, $PROP_{1.0}$ and $PROP_{1.0}$-OPB_{45} and Experiment 2, CONTROL and $PROP_{0.5bis}$. Values for weight represent the mean and SD. Values for DCS represent number of occurrences and percent incidence for each group. In Experiment 1 the incidence of all types of DCS were increased in $PROP_{1.0}$ as compared to $PROP_{1.0}$-OPB_{45}. The incidence of all types of DCS were increased in $PROP_{0.5bis}$ as compared to CONTROL.
* $P < 0.05$ Fisher Exact Test.

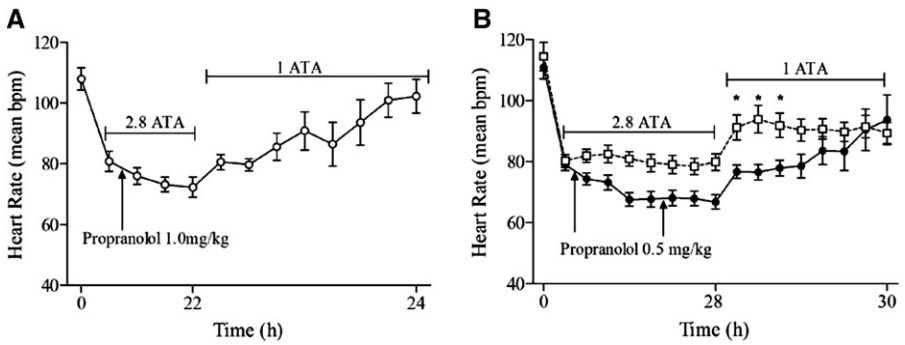

Fig. 1. Average heart rate (bpm) for: A) Experiment 1, $PROP_{1.0}$ (open circles): and B) Experiment 2, $PROP_{0.5}$ (closed circles) and CONTROL (squares). Heart rate was recorded continuously with telemetry. Time points selected for representation are 15 min intervals pre and post drug administration as well as 15 min intervals upon reaching 1 ATA. For the first hour post dive $PROP_{0.5\ bis}$ had a decreased heart rate compared to CONTROL (* $P \leq 0.05$, Two way repeated measures ANOVA with post hoc Bonferonni's test).

incidence and mortality; however, the deleterious effects can be mitigated with an OPB. These findings are contrary to our hypothesis that propranolol would improve DCS outcomes based on the results of previous studies of a beta agonist, isoproterenol. The motivation for this study extends directly from the potential role of propranolol in decreasing metabolic rate and hence CO_2 generation.[22] Thus, while propranolol may extend time to CO_2 toxicity in a DISSUB scenario, the observed increased risk of DCS must be weighed in any risk-benefit analysis.

Mahon et al. reported in previous DISSUB rescue research, that an OPB reduced severe DCS in a 70 kg swine saturation model.[17] We confirm the importance of an OPB in our work by demonstrating a significant improvement in outcomes when propranolol was administered in conjunction with an OPB. Furthermore, we also confirm the deleterious effect of propranolol alone as the incidence of DCS was greater, both compared to the historical controls from this previous study (87% incidence of Type I DCS, 40% incidence of neurologic DCS, and 73% incidence of cardiopulmonary DCS) and significantly higher when compared in a direct randomized control trial in Experiment 2 reported here.

Surprisingly, there is a paucity of literature regarding the effects of antihypertensives and diving safety. In the U.S. alone it is suspected that 80 million adults have hypertension.[23] Although propranolol is an older generation, nonspecific beta-blocker, beta blockers as a class are commonly used in the treatment of hypertension and account for up to 30% of treatment regimens.[10] Current recommendations regarding diving and beta blockers cite the risk of a blunted cardiovascular response to exercise that may limit a diver's physiologic response to unanticipated events.[9] Bove suggested that divers who can maintain a strenuous level of exercise on beta-blockers may be cleared for diving.[5] Furthermore, the U.S. Navy's diving duty standards and submarine duty standards do not limit the use of beta-blockers in these communities.[26] Importantly, none of these resources cite an increased risk of DCS as a basis for caution and the assumed scenarios for these recommendations are based on controlled diving and submarine operations.

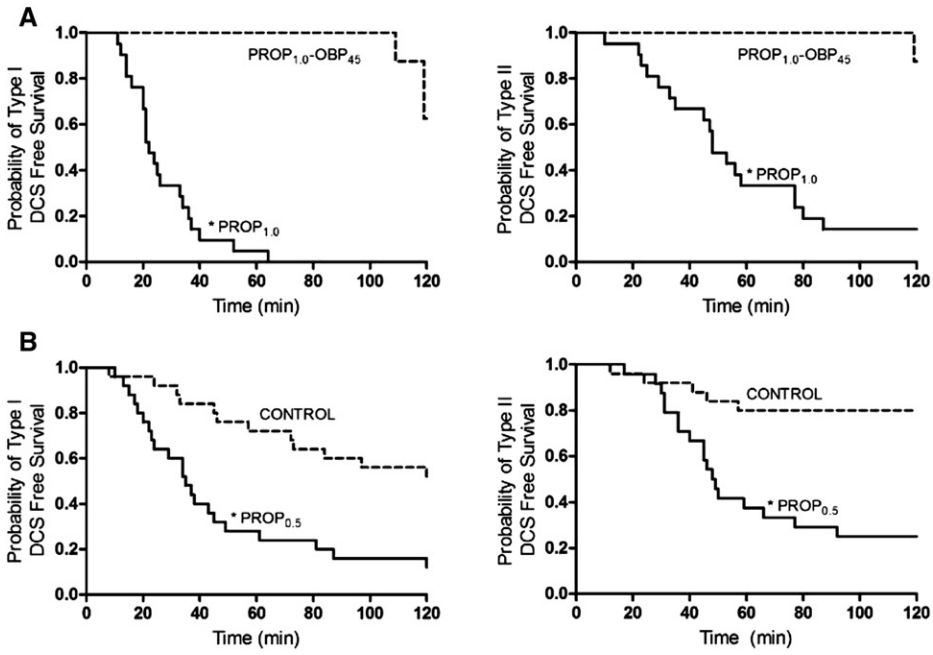

Fig. 2. Kaplan-Meier Curves for the probability of Type I (column 1) and Type II DCS (column 2) free survival over time for A) Experiment 1, and B) Experiment 2. Occurrence of Type I and II DCS were recorded to the nearest minute during the 2-h observation window after dropout from a 2.8 ATA saturation dive. A) Experiment 1: The probability of DCS I and II free survival was significantly greater for $PROP_{1.0}$-OPB_{45} vs. $PROP_{1.0}$ (*$P = 0.0001$ and $P = 0.0005$, log-rank). B) Experiment 2: The probability of DCS I and II free survival was greater for CONTROL vs. $PROP_{0.5}$ (*$P = 0.0003$ and $P = 0.0002$, log-rank).

Although defining the mechanism for propranolol's effects on DCS incidence was not a focus of this work, we postulate reasons as to why beta-antagonists may increase DCS incidence and mortality. Propranolol causes circulatory disturbances including decreased cardiac output and tissue perfusion which may in turn affect DCS incidence by changes in nitrogen elimination.[13] Koteng and Brubakk demonstrated in their swine model of DCS that reducing peripheral blood flow and disrupting the pattern of inert gas elimination in decompression lead to an earlier and greater production of bubbles.[11] Conversely, a study of negative pressure breathing, which increases cardiac output, was associated with increased nitrogen elimination.[14]

Bai et al. analyzed heart rate series to gain insight into autonomic tone.

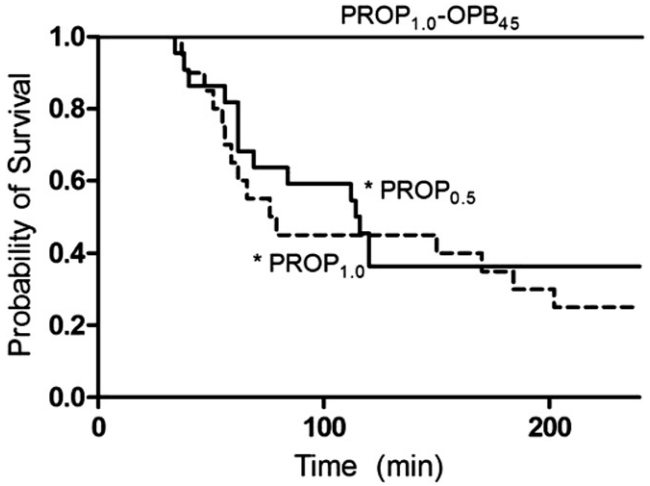

Fig. 3. Kaplan-Meier Curves for the probability of survival over time for $PROP_{1.0}$-OPB_{45}, $PROP_{0.5}$, and $PROP_{1.0}$. Mortality was recorded to the nearest minute during the 24-h observation window after dropout from a 60 fsw saturation dive. No deaths occurred after 220 min postdive. The probability of survival was significantly greater for $PROP_{1.0}$-OPB_{45} vs. $PROP_{0.5}$, and $PROP_{1.0}$ (Bonferroni corrected threshold = 0.02, $*P \leq 0.005$).

Using a swine model of DISSUB dropout they revealed that in cases of cardiopulmonary DCS the parasympathetic tone remains elevated and the sympathetic tone is decreased.[1,2] An associated decreased cardiac output may lead to increased mortality from DCS due to a compromised response to right ventricular failure from increased pulmonary artery pressures in the setting of cardiopulmonary DCS. Large doses of VGE are always followed by a decrease in cardiac output, arterial hypotension and death.[3] The observation of decreased heart rate upon decompression in the propranolol groups when compared to control animals in this study would suggest that cardiac output was likewise decreased. By furthering sympathectomy with propranolol, the necessary increase of inotropy and chronotropy to compensate for the failing right ventricle appears to outweigh the benefit of decreased myocardial oxygen consumption contributing to the increased mortality.

Lastly, though propranolol in the setting of reactive airway disease may impede catecholamine induced bronchodilation, there was no evidence of reactive airway disease in this study. There is some literature supporting the benefit of bronchodilation in reducing DCS incidence. Specifically, terbutaline reduced DCS incidence in rabbits[6] and theophylline decreased DCS in guinea pigs.[13] While both of these drugs are bronchodilators, they are also vasodilators and to some extent positive inotropes. Thus, the decrease in DCS is likely due to enhanced tissue inert gas washout from increased peripheral blood flow rather than bronchodilation. Even if propranolol did induce mild bronchoconstriction it would have very little effect on the elimination of a low solubility inert gas such as nitrogen, except in the presence of a shunt.[30]

Despite the increased DCS incidence with propranolol and the postulated mechanisms, we showed that an OPB mitigates the deleterious effects of propranolol. The inert gas that accumulates during a saturation dive generates intravascular and autochthonous bubbles with decompression, ultimately leading to impaired perfusion of vital tissues. When the inert gas burden is reduced through an OPB, the probability of DCS is either eliminated or significantly attenuated.[8,16,17] Our results support that when an OPB is administered, the harmful effects of propranolol are mitigated.

An important caveat should be noted when assessing the generalizability of our results. Our study captures a unique simulated DISSUB scenario and caution should be used when applying these findings to other diving situations. For example, the timing of propranolol administration in our study was purposefully limited to after 21 h of bottom time to ensure its delivery after saturation was achieved. In an actual DISSUB scenario propranolol would likely be given early to prevent CO_2 toxicity. This early dosing may actually be protective in the setting of increased pressures as it may slow the 'on-gassing' of inert gases. There also exists the possibility for DISSUB survivors to take propranolol while awaiting rescue and then to 'reverse' the effects with a pharmacologic agent such as dobutamine or glucagon prior to escape or rescue.

Furthermore, propranolol is a nonselective $beta_1$ and $beta_2$ adrenergic antagonist. This medication was chosen to expand upon research supporting use of propranolol to limit CO_2 toxicity in a DISSUB.[22] Propranolol as a nonselective adrenergic antagonist will block the circulating catecholamines active during DCS that act at alpha and beta adrenergic receptors. It is possible that a newer generation beta selective antagonist, such as atenolol, would affect DCS outcomes differently. Or a newer generation beta antagonist with peripheral vasodilatory properties such as carvedilol (with some alpha blocking activity), acebutolol (intrinsic sympathomimetic activity), or nebivolol (associated with increased nitric oxide release) may differentially impact DCS risk[28] by improving perfusion to compromised tissues. Nebivolol, through its activation of nitric oxide (NO) synthase, is especially intriguing as a potential adjuvant for DCS as NO has been shown to prevent bubble formation.[31]

Lastly, another important consideration of our work may be the extrapolation of our IV dosing as compared to the oral dosing of propranolol that would be provided in a DISSUB scenario. Oral dosing could not be reliably administered in our swine saturation model. Conscious of the unique pharmacokinetics associated with IV dosing, we completed a dose response study to titrate propranolol to the same percent decrease in heart rate and half-life that is reported in human studies;[21,22] however, we were not able to control for the more efficient hepatic extraction and loss of the active metabolite 4-hydroxypropranolol that may be seen in IV dosing vs. oral dosing.[24] All of these scenarios were not examined in our experiment and additional research should be designed to specifically address these questions.

A thorough risk benefit analysis should occur before recommending the administration of propranolol in a DISSUB scenario where decompression is needed, especially when an OPB is unavailable. The effects of beta blockers during recreational, commercial, and military diving deserve further exploration.

ACKNOWLEDGMENTS

The views expressed in this article are those of the author and do not necessarily reflect the official policy or position of the Department of the Navy, Department of Defense, nor the U.S. Government. This work was funded by NAVSEA work unit number 06037N.0000.000.A0902. The study protocol was reviewed and approved by the WRAIR/NMRC Institutional Animal Care and Use Committee in compliance with all applicable Federal regulations governing the protection of animals in research.

The authors declare that they have no conflict of interest.

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