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Ascent rate, post-dive exercise, and decompression sickness in the rat

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Pollard GW, Marsh PL, Fife CE, Smith LR, Vann RD. Ascent rate, post-dive exercise, and decompression sickness in the rat. Undersea Hyperbaric Med 1995; 22(4):367–376.—The effects of ascent rate and post-dive exercise on the incidence of decompression sickness (DCS) were investigated in six groups of 20 rats exposed for 2 h at a pressure equivalent to 240 feet of sea water (fsw; 735 kPa). Ascent rates were 30, 45, and 60 fsw/min (92, 138, 184 kPa/min), and the rats either rested after the exposure or exercised by walking for 30 min on a treadmill at 1.6 m/min. Post-dive signs included respiratory distress, difficulty walking, paralysis, and death. DCS was scored as non-fatal at 30 min post-dive or fatal at any time. Analysis by ordinal logistic regression indicated more DCS with post-dive exercise ($P = 0.0112$) and at 45 ($P = 0.0011$) and 60 fsw/min ($P = 0.0001$) compared to 30 fsw/min. Survival analysis suggested earlier death at 60 fsw/min compared to 30 fsw/min ($P = 0.0006$). Similar effects have been reported for the less severe DCS that occurs in humans.

decompression sickness, rats, ascent rate, post-dive exercise, venous gas emboli, cardiopulmonary collapse, arterial gas emboli, logistic regression, survival analysis

Rapid decompression rate and post-decompression exercise are commonly accepted as factors that affect the risk of decompression sickness (DCS) in animals and humans after diving and during altitude exposure, but data documenting these effects are limited and often ambiguous (1). To provide a more quantitative understanding, we designed a prospective study of post-dive ascent rate and exercise using rats as experimental subjects. Our working hypothesis, suggested by existing data (1), was that the DCS incidence would increase with ascent rate and post-dive exercise. We found support for this hypothesis and discuss our results in relation to previous experience.

MATERIALS AND METHODS

One hundred and twenty male Sprague–Dawley rats were delivered to the Duke University Medical Center vivarium where they were cared for according to accepted prin-

ciples, with food and water available ad libitum (2). The animals were 2 mo. old upon arrival and were used within 1–3 days to minimize the variation in weight that has a recognized effect on decompression outcome (3,4). Experiments began at 0830–0845 h to minimize diurnal variation in decompression outcome (5).

Thirty minutes before an experiment, 10 rats were weighed and numbered for identification and placed in separate wire-cage compartments within a hyperbaric chamber. After compression at 60 feet of seawater (fsw)/min (184 kPa/min), the animals were exposed for 2 h at an air pressure equivalent to 240 fsw (735 kPa). Two hours is sufficient to saturate air-breathing rats with nitrogen (6,7). Decompression took place at a uniform rate of 30, 45, or 60 fsw/min (92, 138, or 184 kPa/min).

Compression and decompression were controlled by a technician according to tables of appropriate depth at 30-s intervals. The chamber was continuously flushed with air at a predetermined rate to replace metabolically consumed oxygen and to remove carbon dioxide. This maintained an air atmosphere at a temperature of 27°C. The temperature rose to 33°C during compression, fell to 16°C during decompression at 30 fsw/min, and to 14°C during decompression at 60 fsw/min.

Forty rats were tested at each of the three ascent rates with half the rats at rest during the post-dive period and the other half exercising. During 12 experimental days, the rats were assigned at random to ascent rate and exercise in groups of 10 according to the block design of Table 1. After decompression, the five rats assigned to exercise were transferred from the dive cage into separate compartments of a motor-driven cylindrical cage. Transfer took 3 min, after which the cage was rotated for 30 min such that the rats walked at 1.6 m/min. The five rats in the dive cage remained at rest. Because only 10 rats could be exposed in each experiment, the entire design was replicated 4 times in blocks of 30 rats (Table 1). Thus, the independent variables were block, ascent rate, and exercise level. We sought to minimize the effect of the covariate, weight, by using rats of similar age and weight.

The resting and exercising animals were observed for fatal DCS during a 30-min period after transfer, and the time to death was recorded for those that expired. Death was judged to have occurred when all movement ceased, including signs of respiration. At the end of the 30-min observation period (33 min post-dive), both exercising and resting animals were scored for disturbances in gait. The scoring protocol was a variation of the protocol developed by Philp and Gowdey (3) and modified by Powell (8,9). This protocol is shown in Table 2. The gait score at 30 min was tested by ordinal logistic regression whereas time to death was assessed by survival analysis. These methods are described in the appendix. Significance was taken at $P < 0.05$.

RESULTS

Signs exhibited by the rats included respiratory distress, difficulty walking, paralysis, and death. There were no deaths during the 3-min transfer period. Respiratory distress began shortly after decompression and lasted 5–20 min. Many animals recovered from the signs exhibited, although some expired. Three were found dead in their cages the next day. These are indicated as >30 in Table 1.

The raw data are shown in Table 1 and include gait score at 30 min, time to death, and rat weight. Table 2 shows the counts of animals having each gait score. Since only 24 animals had scores of 1–4, these scores were compressed into a single category called non-fatal DCS at 30 min. The compressed scoring system had three categories: no DCS, non-fatal DCS at 30 min, and fatal DCS. The category non-fatal DCS at 30 min underestimated the total non-fatal DCS as some animals exhibited transient signs at other times.

Table 1: Experimental Design and Results[a]

Block	Day	Rate		Rest					Exercise				
1	1	45	Score	0	5	0	5	5	0	5	4	5	1
			Time		6		4	7		9		2	
			Wgt	266	261	267	264	259	265	260	260	268	266
	2	30	Score	0	0	0	0	5	5	0	0	1	0
			Time					4	7				
			Wgt	275	282	283	278	250	288	275	273	271	276
	3	60	Score	5	5	5	5	5	5	5	5	5	5
			Time	11	2	4	4	8	3	13	1	5	7
			Wgt	314	308	298	296	296	297	307	304	297	326
2	4	45	Score	5	0	1	5	0	0	3	1	5	2
			Time	11			18					8	
			Wgt	277	284	274	272	276	284	279	284	275	283
	5	60	Score	5	0	0	0	1	5	5	5	2	3
			Time	9					1	4	1		
			Wgt	295	285	279	290	284	283	285	291	283	284
	6	30	Score	5	0	0	0	0	5	0	0	0	0
			Time	7					5				
			Wgt	288	296	295	301	299	286	290	296	302	300
3	7	60	Score	0	5	0	5	5	2	5	0	0	5
			Time		7		>30	4		3			6
			Wgt	296	304	292	309	292	295	305	318	294	293
	8	45	Score	0	0	0	0	5	0	3	2	5	5
			Time					3				10	1
			Wgt	329	331	314	307	321	313	321	330	315	340
	9	30	Score	0	0	0	0	0	1	2	0	0	0
			Time										
			Wgt	288	294	285	293	292	291	304	299	303	304
4	10	60	Score	1	1	0	0	0	1	5	1	5	5
			Time							2		8	>30
			Wgt	306	297	292	308	310	315	313	313	319	312
	11	45	Score	0	5	1	0	5	5	5	2	1	0
			Time		9			>30	6	18			
			Wgt	301	306	305	320	309	310	308	319	321	322
	12	30	Score	0	3	0	0	0	5	1	5	0	0
			Time						7		4		
			Wgt	323	325	321	321	315	329	326	328	310	335

[a]Units of rate are fsw/min; score is the DCS gait score defined in Table 2; time is the time of death in minutes; time >30 indicates the animal was found dead the next day; wgt is the rat weight in grams.

Figure 1 shows the observed incidences of fatal and non-fatal DCS at 30 min with their 95% binomial confidence intervals for the six combinations of ascent rate and post-dive exercise. When the incidences were analyzed by ordinal logistic regression, there was significantly more fatal and non-fatal DCS at 30 min with post-dive exercise ($P = 0.0112$) and significantly more at 45 ($P = 0.0011$) and 60 fsw/min ($P = 0.0001$) than at 30 fsw/min. Ordinal logistic regression allowed formal recognition that decompression sickness has gradations of severity rather than being a binary "all-or-nothing" phenomenon.

Table 2: Scoring Protocol for Gait Disturbance Derived from Philp and Gowdey (3) and Modified by Powell (8, 9)[a]

Score	Observation	Count
0	No change	53
1	Occasional limping or favoring of limbs	13
2	Hind limb stiffness; often crawls on front limbs	6
3	Drags one or both hind limbs; possible paralysis	4
4	Unable to walk; lies on back or side	1
5	Dead	43

[a]The count of animals in each category is indicated.

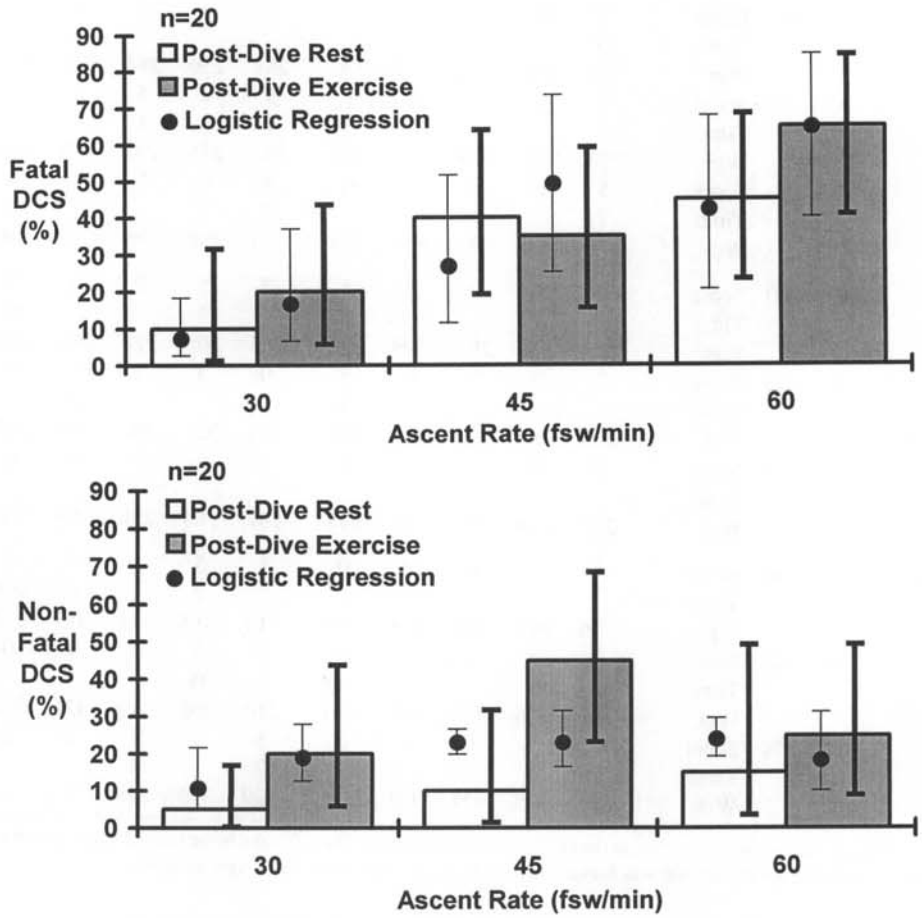

FIG.1—DCS incidence as a function of ascent rate and post-dive activity. Observed results and the DCS probabilities predicted by ordinal logistic regression are shown. *Bars* represent 95% confidence limits estimated by binomial sampling theory or by logistic regression: (*a*) non-fatal DCS at 30 min; (*b*) fatal DCS.

Figure 1 also shows the probabilities and 95% confidence intervals that were estimated by ordinal logistic regression. The regression confidence intervals were often smaller than the binomial confidence intervals, reflecting the greater power of pooled data. The

binomial intervals were based on 20 rats whereas the regression intervals were based on 120 rats.

Figure 2 shows the observed mortality and the mortality estimated by survival analysis for the three ascent rates as a function of time to death. Death occurred earlier as the ascent rate increased. Ascent rate was significantly associated with time to death for 60 fsw/min as compared to 30 fsw/min ($P = 0.0006$) but not to 45 fsw/ min. The three animals found dead in their cages the next day were censored at 30 min, i.e., their time of death was set to the end of the 30-min observation period (type I censoring). Mean mortalities were 15, 38, and 55% at 30, 45, and 60 fsw/min. The number of fatalities in each 40-rat group were 6, 15, and 22.

Mean rat weight was 297 g with a standard deviation of 19 g and a range of 259 to 340 g. Although weight is known to affect DCS outcome in rats (3,4), weight was not significant in the present data when treated as a covariate in ordinal logistic regression and survival analysis (*see* appendix). This was not unexpected as the population was designed to be homogeneous in age, and age is a major determinant of weight for the rat (3).

DISCUSSION

The effects of ascent rate and post-dive exercise we observed on DCS in rats were consistent with the working hypothesis derived from human data. Our observations with nitrogen-saturated rats after 2 h at 240 fsw were similar to the higher DCS incidence in humans with increasing ascent rate after saturation diving (10). The effect of ascent rate to altitude on human DCS is less clear. A retrospective analysis of 14,123 human exposures to altitude was inconclusive (11).

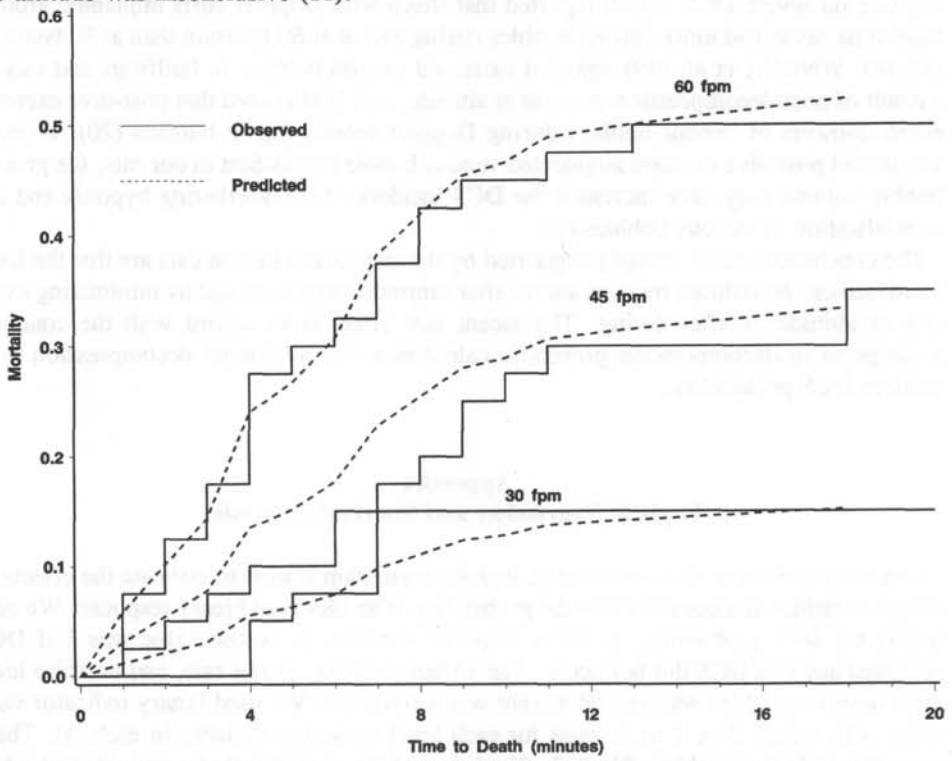

FIG. 2—Mortality as a function of post-dive time and ascent rate. Observed results and the mortality predicted by survival analysis are shown.

There has been only one investigation of post-dive exercise in humans (12). This was a prospective study of 201 no-stop air dives, after which the subjects either rested or exercised by lifting 25 lb (11.3 kg) weights with their arms and legs 4 times/min for 2 h. The DCS incidence was 22% with rest and 47% with exercise. These no-stop dives (24 h at 33–40 fsw [101–123 kPa], 40–60 min at 100 fsw [306 kPa], and 27–36 min at 150 fsw [459 kPa]) were longer than those allowed by modern tables and computers (14-25 min at 100 fsw; 0–5 min at 150 fsw) (13). The influence of post-dive exercise might be less important with the milder modern exposures.

Exercise after altitude decompression was studied extensively in humans during World War II. The most comprehensive investigation was a prospective trial by Gray (described in reference 14) involving 1,100 individual exposures at altitudes of 33,000, 35,000, and 38,000 ft (10,058, 10,667, 11,582 m). Resting subjects had DCS incidences of 5, 10, and 20% at the three altitudes. These incidences increased to 20, 34, and 52% with five deep knee bends and five push-ups every 15 min. This was equivalent to an additional decompression of about 5,000 ft (1,524 m).

Fast ascent and post-dive exercise increase the DCS incidence in both rats and humans, but DCS is generally more severe in rats. Paralysis, unconsciousness, respiratory distress, and death do occur in severe human exposures, however, as demonstrated by early experience in diving and compressed air work (15,16). Human DCS is less severe today because modern dive tables and computers specify relatively mild exposures. Whether DCS is mild or severe, the effects of ascent rate and post-dive exercise seem to be similar for both mild and severe exposures in all species, i.e., they exacerbate the signs and symptoms.

Previous studies suggest a possible mechanism for the effects of ascent rate and post-dive exercise on severe DCS. Smith reported that sheep with Doppler cuffs implanted around their vena cavae had more venous bubbles during ascent at 60 fsw/min than at 30 fsw/min (17,18). Whitaker et al. (19) reported increased venous bubbles in bullfrogs and rats as a result of post-decompression exercise at altitude, and Nishi noted that post-dive exercise elicits showers of venous bubbles during Doppler monitoring in humans (20). If rapid ascent and post-dive exercise augmented venous bubble production in our rats, the greater bubble volume may have increased the DCS incidence by exacerbating hypoxia and the arterialization of venous bubbles (1).

The conclusions most strongly supported by the animal and human data are that the DCS incidence can be reduced by slow ascent after saturation exposure and by minimizing exercise at altitude or after diving. The ascent rate effect is in accord with the common assumption in decompression procedure calculation that additional decompression time reduces DCS probability.

Appendix
Logistic Regression and Survival Analysis

Logistic regression: Conventionally, logistic regression is used to estimate the effects of design variables and covariates on the probability of an observed binary response. We estimated the DCS probability, p, for a response variable, y, whose value was 1 if DCS occurred and 0 if DCS did not occur. The variables block, ascent rate, and exercise level were design variables whereas rat weight was a covariate. We used binary indicator variables with values 0 or 1 to account for each level of design variable in each rat. There were three block variables: Block 2, Block 3, and Block 4. Block 1 was indicated when the three others were 0. For the variable Exercise, 0 indicated post-dive rest, and 1 indi-

cated post-dive exercise. There were two ascent rate variables: Ascent = 45 and Ascent = 60. When both were 0, the ascent rate was 30 fsw/min. We chose to analyze ascent rate as three discrete levels rather than as a continuous variable to avoid assuming a functional form (linearity, etc.) between DCS response and ascent rate. The covariate Weight was treated as a continuous variable. All conditions were compared to a reference condition defined as block = 1, ascent rate = 30 fsw/min, and post-dive rest (Table 1).

Logistic regression is formulated as,

$$p = \frac{1}{1 + e^{-(\alpha + \underline{\beta}\underline{x})}}$$

where $\underline{x} = \{x_1, x_2, \ldots, x_n\}$ is a vector of covariates and design variables, $\underline{\beta} = \{\beta_1, \beta_2, \ldots, \beta_n\}$ is a vector of regression coefficients, α is an intercept, and

$$\underline{\beta' x} = \sum_{i=1}^{n} \beta_i x_i \quad (21).$$

By rearrangement, the logistic equation simplifies to

$$\ln\left(\frac{p}{1 - p}\right) = \alpha + \underline{\beta' x}$$

where the quantity on the left is the natural logarithm of the odds and is called the "logit." In this form, logistic regression has features that are similar to linear regression. The logistic equation is equivalent to the Hill equation,

$$p = \frac{D^{\eta}}{D^{\eta} + \psi}$$

where $\alpha = -\ln(\psi)$ and $x = (\eta/\beta)\ln(D)$.

For each subject, the covariates, $\underline{x}$, and the outcome variable, y, are observed, and a "likelihood" is computed using the logistic equation where likelihood is the probability of an observed outcome (likelihood = p if y = 1; likelihood = [1-p] if y = 0). The parameters α and β_i are estimated by adjusting their values until the likelihood for all subjects (the product of individual likelihoods) is maximized. This defines the best possible correspondence between the observed outcomes and corresponding logistic probabilities and is analogous to minimizing the least squared error in linear regression. The maximum likelihood estimates of the β_i were calculated by iteratively weighted least squares using PROC LOGISTIC in SAS (22). A covariate, x_i, is considered to have a significant effect if its corresponding parameter estimate, β_i, is statistically different from zero by a chi-square test.

Ordinal logistic regression: The dichotomous logistic regression described above may be extended to polytomous ordered outcomes by a method known as ordinal logistic regression (23). The ordered outcomes we observed were no DCS, non-fatal DCS at 30 min, and death. If $p_j = \Pr[Y \leq \int | \underline{x_i}$ is the probability of being in an outcome state less than or equal to state j, then the ordinal logistic model is formulated as

$$\ln\left(\frac{p_j}{1 - p_j}\right) = \underline{\alpha} + \underline{\beta' x}.$$

where $\underline{\alpha} = \{\alpha_1, \alpha_2, .., \alpha_k\}$ is a vector of intercepts. For k+1 states, the probability that the i^{th} animal observation is in state j is

$$\Pr[Y = j \mid \underline{x}_i] = \begin{cases} \Pr[Y \le 1 | \underline{x}_i] & j = 1 \\ \Pr[Y \le j \mid \underline{x}_i] - \Pr[Y \le j - 1 \mid \underline{x}_i] & 1 < j \le k \\ 1 - \Pr[Y \le k] & j = k + 1 \end{cases}.$$

This is equivalent to p(no DCS) + p(non-fatal DCS at 30 min) + p(death) = 1. Non-fatal DCS at 30 min and death have separate intercepts (α_j), but all other parameters (β_i) are the same. The variates and their parameter values are shown in Table 3. The covariate weight was not significant. This was expected as the rats were chosen to be homogeneous in weight to minimize outcome variability due to weight. α_1 is the $\log_e$ odds of non-fatal or fatal DCS vs. no DCS for a resting animal in Block 1 with an ascent rate of 30 fsw/min. α_2 is the $\log_e$ odds of having fatal DCS vs. no DCS or non-fatal DCS at 30 min for the same experimental conditions. The negative sign for the Exercise parameter indicates the increase in $\log_e$ odds of non-fatal and fatal DCS for exercise over rest. The negative sign for the Rate = 45 and Rate = 60 parameters indicates the increase in $\log_e$ odds of non-fatal and fatal DCS for ascent rates 45 and 60 over ascent rate 30 fsw/min.

A significant block effect indicated some variation in experimental conditions between blocks, which might have been due to differences in experimental setup, procedure, or animal susceptibilities (Table 1). Blocking is a standard method for reducing or accounting for unknown effects across experimental conditions. Because only 10 animals could be tested at one time, they were blocked in groups of 30 and randomized into one of six exercise/ascent rate combinations.

The probability of non-fatal DCS or death was computed for each exercise/ascent rate combination by applying the appropriate parameter values to each rat using the rat's vector of covaraites. The resulting probabilities were averaged over the rats in each exercise/rate combination and are shown in Fig. 1.

Survival analysis: For binary outcomes that occur at different points in time, the time-to-event is a response of interest that can be analyzed by survival analysis. Kumar (24) has described survival analysis models for analyzing DCS. In our study, the subjects were followed for 30 min after decompression, and the time to fatal DCS was the variable of interest. Not all rats died during the observation period. Those that did not are called censored, i.e., they contribute no information within the observation period.

Table 3: Variates and their Parameter Values

Variable (x_i)	Estimate β_i	χ^2	p-value
α_1	0.6469	1.62	0.2022
α_2	1.6993	10.35	0.0013
Block 2	1.1598	4.70	0.0301
Block 3	1.3928	6.60	0.0102
Block 4	0.9068	2.94	0.0866
Exercise	−0.9634	6.44	0.0112
Rate = 45	−1.5686	10.66	0.0011
Rate = 60	−2.2575	20.59	0.0001

There are a number of formulations of the time-to-event model, most involving the hazard function, $\lambda(t)$. The hazard function is the probability of death in the interval $(t, t+\delta t)$ on the condition that the individual survived until time t. The survival function, S(t), is the probability that a subject survives longer than time t. S(t) is given by $S(t) = \theta^{-\Lambda(t)}$ where

is the cumulative hazard up to time t.

To determine the effect on survival of the experimental conditions (ascent rate and post-dive exercise) and covariates (rat weight), we used Cox's formulation of the hazard function with $\lambda(t;x) = \lambda_0(t)*\exp(\beta x)$ where x is a vector of experimental conditions and covariates and $\lambda_0(t)$ is the hazard function when all conditions and covariates are in their baseline state (25). As defined above, the baseline state exists when block=1, rate = 30 fsw/min, and post-dive rest. The event-free survival is then $S(t;x) = S_0(t)^{\exp(bx)}$, where $S_0(t)$ is the underlying event-free survivorship function corresponding to $\lambda_0(t)$. $S_0(t)$ and the β_i are estimated by maximum likelihood techniques using PROC PHREG in SAS (26).

To estimate the event-free survivorship function for a given subject, the exponent, $\exp(\beta x)$ of $S(t;x) = S_0(t)^{\exp(bx)}$ is calculated for each rat and applied to the underlying $S_0(t)$. These curves are averaged for the rats in each ascent rate group. Data presented in Fig. 2 are the cumulative event distributions, $F(t)=1-S(t)$.

A basic assumption in the formulation of survival analysis described above is that all animals will die if observed long enough (25). This is only true in decompression for the most severe exposures. More often, as in our study, only a fraction of the subjects exposed are affected. Although this restrictive formulation detected a statistically significant ascent rate effect, a more general approach is desirable. Such an approach assumes that the underlying hazard decreases to zero so that the cumulative hazard is constant after some time, t. This approach was explored by Weathersby et al. (27).

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