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A ternary model of decompression sickness in rats

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ABSTRACT

Background: Decompression sickness (DCS) in rats is commonly modelled as a binary outcome. The present study aimed to develop a ternary model of predicting probability of DCS in rats, (as no-DCS, survivable-DCS or death), based upon the compression/decompression profile and physiological characteristics of each rat.
Methods: A literature search identified dive profiles with outcomes no-DCS, survivable-DCS or death by DCS. Inclusion criteria were that at least one rat was represented in each DCS status, not treated with drugs or simulated ascent to altitude, that strain, sex, breathing gases and compression/decompression profile were described and that weight was reported. A dataset was compiled ($n=1602$ rats) from 15 studies using 22 dive profiles and two strains of both sexes. Inert gas pressures in five compartments were estimated. Using ordinal logistic regression, model-fit of the calibration dataset was optimised by maximum log likelihood. Two validation datasets assessed model robustness.
Results: In the interpolation dataset the model predicted 10/15 cases of nDCS, 3/3 sDCS and 2/2 dDCS, totalling 15/20 (75% accuracy) and 18.5/20 (92.5%) were within 95% confidence intervals. Mean weight in the extrapolation dataset was more than 2 SD outside of the calibration dataset and the probability of each outcome was not predictable.
Discussion: This model is reliable for the prediction of DCS status providing the dive profile and rat characteristics are within the range of parameters used to optimise the model. The addition of data with a wider range of parameters should improve the applicability of the model.

1. Introduction

Animal models offer alternatives to human studies into decompression sickness (DCS) that are both ethically preferable for speculative research and logistically convenient. Prawns, mice, rabbits, dogs, goats, pigs and primates have all contributed to mankind's understanding of DCS but the leading role in animal model research surely belongs to the laboratory rat, *Rattus norvegicus*. Pressure exposures designed to elicit DCS in only a proportion of rats vary in depth, time at maximum exposure, breathing gas, rates of compression/decompression and other parameters. Treatments and/or risk factors are then typically evaluated by the degree of difference in the proportion of animals that are diagnosed with DCS following decompression [1].

DCS in the rat has been variously defined and diagnostic criteria include survival time, [2–4] observable signs such as walking difficulties [3,5–14], paralysis, [5–19] rolling in a rotating cage [5–9,12,13,15,16,20], twitching/convulsions [5–9,12,13,15,16] and/or respiratory distress [5–7,9–11,13,14,17–19]. Objective measures have been proposed, in particular observable or audible bubble grades [10,21,22]. Only rarely have objective measures been correlated with subjective observer agreement. Recently a

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promising grip-score test was found significantly associated ($p=0.004$) with observable signs of what was assumed to have been DCS [23]. Unexpectedly, based upon the correlation between loss of grip strength and perceived DCS, Buzzacott et al. discovered the post-decompression probability of any asymptomatic rat having DCS was 0.5. The precise diagnosis of DCS in the rat, therefore, remains a desirable goal.

In almost all studies to date DCS in the rat has been modelled as either the probability of no-DCS vs. DCS [9,12,15,16,24,25], or of Dead vs. Alive [4,11]. Occasionally both models will be sequentially used in the same study but without delineating the relative probabilities of each DCS status [5,26]. To our knowledge only one study has used ordinal logistic regression for ternary DCS outcomes in rats, for an assessment of the effects of ascent rate and post-dive exercise [27]. In this study Pollard and colleagues used ordinal logistic regression to model the probability p of a DCS outcome state j (either no-DCS, survivable-DCS or death), given i independent covariates $x_{1:n}$ with respective coefficients $\beta_{1:n}$, as

$$Ln\left(\frac{p_j}{1-p_j}\right)=\underline{\alpha}+\sum_{i}^{n}\beta_i x_i \tag{1}$$

where $\underline{\alpha}=[\alpha_1, \alpha_2, \ldots, \alpha_k]$ is a vector of intercepts (one less than the number of outcome states). For $k+1$ states, the probability of the i^{th} observation being in state j is given in Eq. 2.

$$\Pr[DCS=j|x_i]=\begin{cases}\Pr[DCS\le 1|x_i] & j=1\\ \Pr[DCS\le j|x_i]-\Pr[DCS\le j-1|x_i] & 1<j\le k\\ 1-\Pr[DCS\le k] & j=k+1\end{cases} \tag{2}$$

The present study aimed to develop a ternary model of predicting the probability of DCS in rats, (as either no DCS, survivable DCS or death), based upon compression/decompression profile-dependent inert gas compartment pressure estimates, after adjustment for sex, weight and strain.

2. Methods

An electronic literature search identified protocols with compression/decompression profiles that elicited a predictable proportion of DCS greater than 0 but less than 100%. From these, studies classifying decompression outcomes as no-DCS (nDCS), survivable-DCS (sDCS) or death by DCS (dDCS) were identified. The inclusion criteria for the rats in each study were that at least one rat was represented in each DCS classification post-decompression to 1 ATA, that the rats were not treated (or pre-treated) with experimental drugs (only control rats were included in our dataset), that the strain, sex, breathing gases (only oxygen:nitrogen combinations) and compression/decompression profile were described and that either individual weights or a group mean with relatively small standard deviation ($<15\%$ of the mean) were reported. Where only one of these parameters was unclear in any published paper then the original authors were contacted with a request to clarify missing details. Only 100% complete data were accepted into the dataset. As soon as the dataset contained in excess of 1600 rats then further inputting was curtailed. By this stage the dataset was comprised of 15 studies [2–4,7,10,13,17,18,20,22,28–32] using 22 different dive profiles and two strains of rat; Sprague-Dawley ($n=1421$, 89%) and Wistar ($n=181$, 11%).

Diagnostic criteria for DCS classification was either explicitly stated in each paper (i.e. based on observed respiratory distress or motor ataxia) or else implied by gas emboli score [4,22]. The final model was tested both with and without rats diagnosed by bubble score to assess homogeneity of the dataset. From the description of each compression profile ambient and gas partial pressures in msw at 10 s intervals or less were calculated in MS Excel. Using the R package SCUBA stepwise inert gas pressures (in ATA) in 17 Bühlmann compartments (ZH-L16A) were then estimated [33,34]. As rats are thought to saturate in less than 90 min [6,26,35] only compartments 1–4 (including 1b), with nitrogen half-times of 4.0, 5.0, 8.0, 12.5 and 18.5 min respectively, were included in the initial model [34] shown in Eq. (3). Longer total saturation times have been proposed but are the exception [36]. From the estimated compartment inert gas pressures two parameters were estimated. The maximum positive difference for each compartment between compartment inert gas pressure and inspired inert gas pressure (in ATA) during ascent ($Max_{1\text{-}4}$: a measure of positive pressure gradient for off-gassing) and the maximum positive difference between compartment inert gas pressure and ambient pressure (in ATA) during ascent ($Bubble_{1\text{-}4}$: a measure of bubble production capacity). Model optimisation is described below, in Section 2.1.

$$\begin{aligned}Logit[\Pr(DCS=j|x_i)]=\alpha_j+\beta_1 Weight_i+\beta_2 Strain_i+\beta_3 Sex_i+\beta_4 Dive_i+\beta_5 Exercise_i\\ +\beta_6 Max1_i+\beta_7 Max1b_i+\beta_8 Max2_i+\beta_9 Max3_i+\beta_{10} Max4_i+\beta_{11} Bubble1_i+\\ \beta_{12} Bubble1b_i+\beta_{13} Bubble2_i+\beta_{14} Bubble3_i+\beta_{15} Bubble4_i\end{aligned} \tag{3}$$

where DCS was nDCS=0, sDCS=1 and dDCS=2. Weight=the weight in grams, Strain was either Sprague-Dawley (0) or Wistar (1), Sex was 0 for male and 1 for female, Dive was the stratification variable for which particular compression/decompression profile each rat underwent, Exercise was if each rat exercised in a rotating wheel either during or after the dive, where no exercise=0 and with exercise=1. The final model was optimised by logistic regression and backwards elimination of least significant parameters. At $n=1602$ rats in the calibration dataset there was an initial mean of no less than 27 rats per parameter in each of the three outcome classes, nearly triple the recommended minimum [37].

To validate the resultant model for interpolation two control groups (from previous experiments) of 10 male (age 11 wks, 401 ± 18 wt) and 10 female (age 14 wks, 266 ± 22 wt) rats were combined. These 20 rats had been compressed and decompressed according to the protocol (Fig. 1) described by Eftedal, vide infra [22]. This profile, but not these rats, was included in the calibration dataset. To validate the resultant model for extrapolation 119 control rats from four previous experiments (109 male and 10 female) were combined into a single dataset, including 20 Wistar (384 ± 15 wt) and 99 Sprague-Dawley (428 ± 60 wt), age 10–13 wks.

All rats in both validation datasets were obtained from Janvier SAS (Le Genest St Isle, France) at age 10 weeks. The rats were housed for at least one week in the University vivarium in standard conditions, (mean temperature 21.2 °C $\pm$0.2 SD, relative humidity 27% $\pm$16% SD, 12 h light:dark cycle), during which they had access to rat chow and water ad libitum. Each rat was weighed on the day of diving and then compressed in a 170-litre Comex hyperbaric chamber in groups of up to seven at a time. All dives commenced in the morning after 8 am.

For the interpolation profile compression with air occurred at the rate of 2 ATA min^{-1} to a pressure of 7 ATA (60 msw) and maintained for 45 min. At the end of the exposure period these rats were decompressed linearly to the surface at a rate of -0.5 ATA min^{-1}.

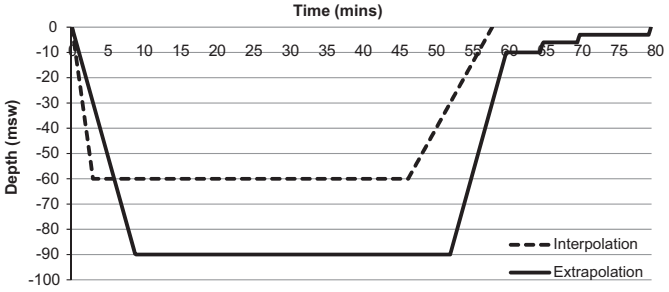

Fig. 1. Time–pressure profiles of the interpolation and extrapolation datasets.