

Predicting risk of decompression sickness in humans from outcomes in sheep

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Ball, Robert, Charles E. Lehner, and Erich C. Parker. Predicting risk of decompression sickness in humans from outcomes in sheep. *J. Appl. Physiol.* 86(6): 1920–1929, 1999.—In animals, the response to decompression scales as a power of species body mass. Consequently, decompression sickness (DCS) risk in humans should be well predicted from an animal model with a body mass comparable to humans. No-stop decompression outcomes in compressed air and nitrogen-oxygen dives with sheep ($n = 394$ dives, 14.5% DCS) and humans ($n = 463$ dives, 4.5% DCS) were used with linear-exponential, probabilistic modeling to test this hypothesis. Scaling the response parameters of this model between species (without accounting for body mass), while estimating tissue-compartment kinetic parameters from combined human and sheep data, predicts combined risk better, based on log likelihood, than do separate sheep and human models, a combined model without scaling, and a kinetic-scaled model. These findings provide a practical tool for estimating DCS risk in humans from outcomes in sheep, especially in decompression profiles too risky to test with humans. This model supports the hypothesis that species of similar body mass have similar DCS risk.

risk prediction; allometric scaling; decompression illness; hyperbaric; diving

DECOMPRESSION SICKNESS (DCS) can affect divers, caisson workers, aviators, and astronauts after a change from a higher to a lower ambient pressure. Symptoms and signs can include painful joints, neurological dysfunction, skin rash, and, in some cases, cardiopulmonary collapse (4). The accepted cause of DCS is tissue injury resulting either directly or indirectly from the formation of bubbles of inert gas during decompression (5). Application of survival analysis to DCS incidence data of humans has led to successful risk prediction under decompression conditions that do not carry high DCS risk (12, 14, 16). The most successful of these models, USN93 (10), is an excellent predictor of DCS risk in a variety of dives that use air and other nitrogen-oxygen breathing gases. However, there are situations (such as escape from a disabled submarine) for which it is necessary to estimate the risk of a profile that is outside the range of known human data and for which human trials are prohibited.

Extrapolating DCS risk predictions to humans under severe decompression conditions by using models derived from low-risk data, such as USN93, has proven inadequate. For example, USN93 substantially under-

predicts the DCS risk of deep no-decompression stop air dives not included in its calibration data, as shown in Fig. 1. An approach to solving this problem is to use animal decompression data, which can include high-DCS incidence exposures. In this paper, we introduce a method for combining animal data with human data under a common probabilistic model of DCS risk to predict human DCS incidence from high-risk profiles.

Initial work, by Boycott and colleagues (3), to predict decompression responses in humans from those in animals was conducted at the beginning of this century. Goats were used to develop a decompression model for application to human divers breathing compressed air. This work compared observed outcomes in goats after a dive simulated by hyperbaric exposure with the calculated partial pressures of inert gas in a parallel-compartment model of tissue inert-gas exchange. Safety thresholds for the theoretical tissue compartments were developed based on the maximum calculated “overpressure” that could be tolerated before the decompressed goats exhibited signs of DCS. On the basis of subsequent decompression experience in humans (6), this technique was extended to human divers by empirically adjusting the number of compartments, the compartment washout times, and threshold values of symptomatic DCS.

Rates of biological processes in animals are allometric if they are proportional to body mass raised to some power (18). Application of allometric scaling demonstrates that experimental DCS incidence in animals scales as a function of species body mass (2, 7). However, it remains to be shown that it is possible to use animal DCS outcomes from a particular dive profile to accurately predict the risk of DCS in humans from the same profile.

We hypothesized that, because the DCS risk models underlying survival analysis of DCS data incorporate information on the physiology of decompression, this method could be applied to predict the risk of DCS in humans from the risk observed in decompressed animals for specific dive profiles.

METHODS

Principles of combining human and animal data. Our goal is to demonstrate that the human dose-response relationship can be obtained from the animals through parameters used to adjust or “scale” the animal dose response to that of the human. We first define a probabilistic model of DCS risk that relates the decompression dose (i.e., the pressure history of the dive) to the probability of developing DCS, using methods that have been previously described (12, 14, 16). In these probabilistic models, model parameters are estimated from the outcome data (i.e., DCS or no DCS) by using the method of maximum likelihood rather than representing values ob-

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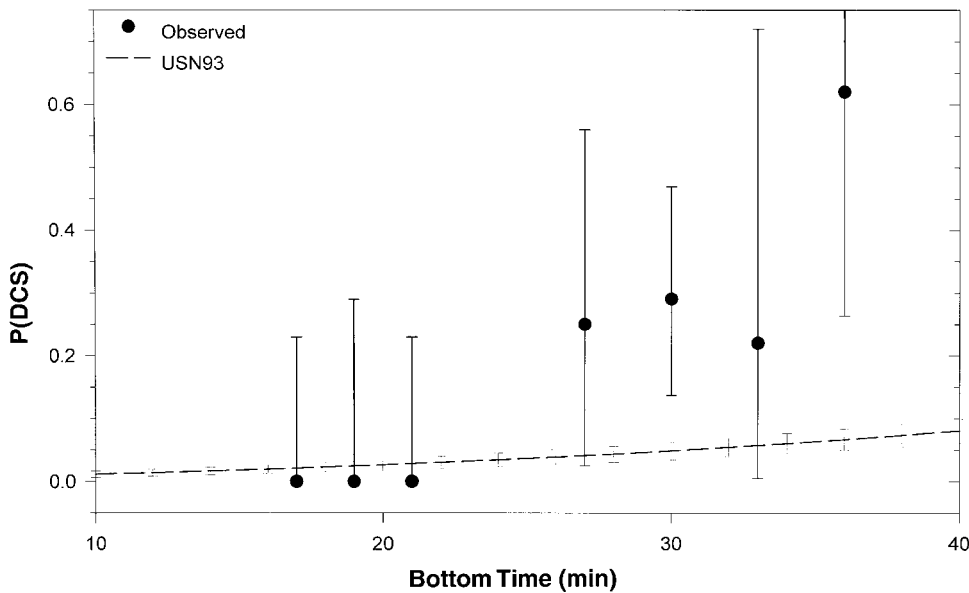


Fig. 1. Model ability to predict decompression sickness (DCS) observed incidence (●) in validation data for 150-fsw no-decompression air dive. Model USN93 substantially underpredicts DCS occurrence (dashed line). Error bars are 95% confidence intervals on prediction for model and binomial 95% confidence interval for observed incidence. *P*, probability.

tained from physiological experiments. Our model differs from those that use a single species in that we add parameters that allow the model to “adjust” the response, depending on which species is represented. In developing this species “scalable” model, we consider three factors that may give rise to divergence of the interspecies dose-response relationships: species differences in tissue gas kinetics, in tissue sensitivity to the presence of bubbles, and in the accuracy of the diagnosis of DCS. Any probabilistic model of DCS risk used for interspecies scaling must be able to account for these differences.

The decompression dose in available data comprises a wide range of pressure profiles. Therefore, determining the similarity of the dose-response relationships requires a method that compares dose response across the pressure-profile range as well as between species. To accomplish this, we first fit the DCS risk model (without the scaling parameters) separately to each species. The log likelihood (LL) of the best fit provides a summary measure of the goodness of fit to the data for each species. In more physiological terms, the LL summarizes the ability of the model to predict the single-species dose-response relationship over the range of pressure profiles represented in the data. We next fit the model to the data set that combines the animal and human data, without differentiating between the two. The scalable model is then fit to the data set that combines the animal and human data, maintaining the identity of the species. The LL of this fit indicates how well the scalable model describes the dose-response relationship of each species, by using common parameters and scaled parameters.

To determine whether the animal and human data can be combined without the need for scaling, we compare, using the likelihood ratio (LR) test, the LL of the nonscaled-model fit to the combined data with the sum of the LLs of the models using the separate species (14). This test determines whether a model with common parameters for both species can describe the dose-response relationship as well as it can with two separate fits. The LR statistic is calculated as

$$LR = -2[(LL_{\text{animal}} + LL_{\text{human}}) - LL_{\text{combined}}] \quad (1)$$

LR is compared with the values of the χ^2 distribution with $k + j - p$ degrees of freedom, where k and j are the number of

parameters of the animal and human models, respectively, and p is the number of parameters of the combined model. If $LR > \chi^2_{(0.95, k+j-p)}$, then we conclude that the separate models provide a better fit to the data than the combined model does, suggesting that the data sets cannot be simply combined without explicitly accounting for species differences.

Next, to determine whether the scalable model provides an improved fit, we compare, again using the LR test, the LL of the scalable model fitted to the combined data with the sum of the LLs of the models using the separate species. This step tests whether combining the data from animals and humans under a scalable model is preferred when compared with the two separate models. In this context, the LR test involves determining whether any additional parameters required in the separate models (beyond those used in the scalable model) are justified by the improvement in the LL of the sum of the two separate models over the LL of the scalable model estimated from combined data. The LR statistic is given by

$$LR = -2[(LL_{\text{animal}} + LL_{\text{human}}) - LL_{\text{scalable}}] \quad (2)$$

If $LR > \chi^2_{(0.95, k+j-m)}$, where m is the number of parameters in the scalable model, then we conclude that the separate models provide a better fit to the data. This suggests that the scaling parameters did not properly or completely account for the species differences. If the $LR < \chi^2_{(0.95, k+j-m)}$, this suggests that the scalable parameters have substantially accounted for the differences in DCS dose response between species. If both the combined and scalable models are preferred over the two separate models, a third LR test can be performed comparing the combined and scalable models.

Modeling DCS risk. The DCS risk model selected for this approach is the model that best fits a large series of air and nitrogen-oxygen (N_2 and O_2 at hyperoxic concentrations) human dives (10, 12). This model is an extension of well-stirred multiple parallel-compartment models with single-exponential inert-gas pressure decay. The present model differs from earlier models developed by Haldane and modified by other investigators (6) in that it uses linear-exponential gas-elimination kinetics (12). The inert-gas washin phase is exponential, and the washout phase can be

linear initially, followed by a return to exponential kinetics. Use of this kinetic flexibility has given rise to the name linear-exponential (LE) model. Instantaneous risk is defined as the weighted sum of compartmental inert-gas supersaturation divided by the ambient pressure. Up to four parameters are estimated from the data for each compartment: G_i is a weighting factor (referred to as the “gain” of the compartment), τ_i is the exponential washout time constant, PXO_i is the gauge pressure at which the switch from linear to exponential kinetics takes place, and Thr_i is the gauge pressure threshold above which inert-gas pressure contributes to DCS risk for the i th compartment. Any number of compartments can be included in the model, although USN93, which is the best-fitting model to a comprehensive set of 3,222 human air and nitrogen-oxygen exposures, required only three compartments (10). The best model is defined as the one with the minimum number of estimated parameters that gives the maximum LL (14, 16). Complete details of the parameter estimation process are given elsewhere (9, 12).

We modified the LE model by constructing explicit scaling parameters for each of these LE model parameters. Mathematically, the scaling parameters all have the same structure. These parameters allow estimation of the main parameter from the animal data with an additive component, the Δ (scaling) parameter, estimated from the human data

$$\tau_{Hi} = \tau_{Ai} + \Delta\tau_{Hi} \quad (3)$$

$$PXO_{Hi} = PXO_{Ai} + \Delta PXO_{Hi} \quad (4)$$

$$\exp(G_{Hi}) = \exp(G_{Ai} + \Delta G_{Hi}) \quad (5)$$

$$Thr_{Hi} = Thr_{Ai} + \Delta Thr_{Hi} \quad (6)$$

where G_{Ai} , τ_{Ai} , PXO_{Ai} , and Thr_{Ai} are estimated from animal data, and ΔG_{Hi} , $\Delta\tau_{Hi}$, ΔPXO_{Hi} , and ΔThr_{Hi} are estimated from human data for the i th compartment. Complete model equations are given in the APPENDIX. Body mass is not considered as a parameter in this model, because body mass data were not available for all human divers.

As indicated earlier, we consider three factors that may give rise to interspecies divergence of the DCS dose-response relationship: differences in gas kinetics, in tissue sensitivity to the presence of bubbles, and in the accuracy of the diagnosis of DCS. The LE model has two estimable parameters (τ and PXO) that explicitly represent the role of inert-gas kinetics in DCS risk. The threshold above which compartmental pressure must rise before that compartment contributes to risk is determined by the Thr parameter. Thr might be interpreted as the “sensitivity” of the tissues represented by that compartment to injury from bubble formation. The G parameter determines the relative contribution of each compartment to the total risk. This parameter provides adjustment for whatever other factors might contribute to DCS risk. As a consequence of these parameter interpretations, we combined differences in DCS diagnosis between animals and humans and differences in species sensitivity to gas bubbles into what we refer to as response scaling, using the G and Thr parameters. This approach involves estimating the kinetic parameters of the model (τ and PXO), without scaling parameters, by using the combined animal and human data set without differentiating between animal and human. At the same time, the response parameters (G and Thr) are estimated from the animal data, whereas their scaling parameters (ΔG and ΔThr) are estimated from differences between the animal and human data. A second approach, kinetic scaling, requires that the response param-

eters (G and Thr) be estimated from the combined data. Concurrently, the kinetic parameters (τ and PXO) are estimated from the animal data, and the kinetic scaling parameters ($\Delta\tau$ and ΔPXO) are estimated from the human data.

If the LR test comparing the LE model with response scaling with the separate animal and human LE models supports the scalable model, we can conclude that the kinetics of DCS are similar for the animal and human data. Similarly, if the LR test comparing the LE model with kinetic scaling with the separate animal and human models supports this type of scaling, we can conclude that the response to decompression dose is similar between species.

DATA

Although many animal species could be used, the sheep was selected as a human surrogate, because its body size and tissue blood flow are similar to those in humans (1, 7, 8). The sheep used in these studies were 22–124 kg, with an overall mean (\pm SD) weight of 78 ± 22 kg (8). Blood flow is thought to be a major determinant of inert-gas uptake and elimination and a major contributor to DCS risk. In mammals, metabolism and tissue blood flow rates scale to the three-fourths power of body mass (18). By having our comparison species' body size and blood flows similar to humans, we felt we would reduce the species differences between the animal and human decompression kinetics. As a result, we expected little difference in the kinetic-parameter estimates of the LE model, but the procedure we have outlined allowed us to test this hypothesis formally. Moreover, DCS is manifested in sheep by limb lifting and by neurological and cardiopulmonary abnormalities that are roughly analogous to the primary manifestations of DCS in humans. These similarities should increase the likelihood of successful scaling of DCS risk to the human diver.

Sheep underwent hyperbaric exposures in a high-pressure chamber at the University of Wisconsin Biotron to simulate dive profiles. Data of no-stop sheep air dives and DCS outcomes were obtained by review of logbooks and recorded in detail in a previous report (8). All dives were conducted dry with freestanding sheep in the hyperbaric chamber. The subjects were observed continuously, beginning with rapid decompression to ambient pressure until at least 4 h after surfacing and again at 24 h. The data comprise dive profile and outcome information, including whether DCS occurred, the type of DCS (limb, central nervous system, or cardiopulmonary), and information about the latency of DCS after decompression. The temporal information includes the times of first occurrence of possible DCS (T_1), probable DCS ($T_{1.5}$), and the earliest time that the sheep definitely displayed symptomatic DCS (T_2).

Human data represent a subset of dives, which were selected to match the sheep dive profiles, from the original primary decompression database maintained at the Naval Medical Research Institute (NMRI) (15, 17) and additional dive trials conducted at the Naval Submarine Medical Research Laboratory (NSMRL; Groton, CT), NMRI, and the Naval Experimental Diving Unit (NEDU; Panama City, FL) (11). (Note: NEDU, NMRI, and NSMRL reports are available from the National Technical Information Service, 5285 Port Royal Rd., Springfield, VA 22161, or on the internet at www.ntis.gov.) The dives were conducted under a variety of conditions and included both wet and dry exposures. Information contained in the human database consists of dive profile and outcome, including whether or not DCS occurred, and the time of DCS occurrence. The human temporal information differed somewhat from the sheep and included the latest time that the diver was definitely normal (T_1) and the earliest

time the diver was definitely considered to have DCS (T_2). Divers were typically under direct medical observation for 2 h after surfacing and then again for a brief time between 18 and 24 h postdive. Both sheep and humans made multiple dives, usually with at least 48-h recovery between dives.

The time of DCS for sheep and humans is represented as an occurrence density function (ODF) (12) in Fig. 2. The ODF for a single DCS case is constructed by spreading the risk for that case uniformly over the time interval between T_1 and T_2 associated with the case. The ODF is zero until T_1 , then rises to $1/(T_2 - T_1)$, and then falls back to zero at T_2 . The ODF for all cases is calculated by summing the vertical distances for all individual ODFs. The total area within each time interval is added up and divided by the length of the time interval (in the case of Fig. 2, the time interval is 1 h), and this average value is assigned to the entire interval.

The ideal test of the hypothesis is under conditions in which the human and sheep are exposed to the identical pressure profile. This approach allows for a direct comparison of the dose-response curves. Any differences in parameter estimates between species (i.e., any nonzero scaling parameters) can be interpreted as being due to species differences and not from a bias introduced by the extrapolation between dose-response curves. To meet this criterion as closely as possible, we selected sheep and human dives with overlapping bottom times and matched those dives as closely as possible by depth. Sheep dives from dive duration groups of 30, 60, and 240 min (8) were found to match human dive profiles. For human data, the original data set name and the dive profiles extracted from those data sets (11, 15, 17) after being matched with a sheep dive profile are given in Table 1.

Many of the human dives were done on gas mixes containing 12–40% oxygen, with the balance nitrogen. In those cases, the equivalent air depth was used for matching. All sheep and human dives were no-stop dives, although ascent rates varied slightly (sheep: 17–40 feet of seawater (fsw)/min, human: 25–67 fsw/min). The distribution of sheep and human dives and DCS cases in 18 depth-time categories is shown in Table 2. Dives matched nearly exactly by bottom time and within 10

Table 1. Sources of human decompression data

Original Data Set Name	Extracted Profiles	Ref. No.
DC4D	169, 170, 180, 181	11, 17
EDU1351NL	30	11, 15
EDU849LT	8–21	11, 15
EDU885A	29, 30, 75, 77, 78, 79	11, 17
NMR8697	14–66, 74–86, 91–102, 110–149, 158–212, 217–229	11, 17
NMRNSW	29–31	11, 17

fsw of depth for most of the dives. The matching process resulted in the selection of a total of 463 human dives with 21 DCS cases (4.5%) and 20 marginal cases (4.3%), and 394 sheep dives with 57 DCS cases (14.5%) and 53 marginals (13.5%). For humans, a marginal case consisted of “transient aches or pains following a dive that seem related to the pressure exposure, but were not of a severity or persistence to warrant treatment” (12). A sheep that exhibited signs suggesting a diagnosis of probable DCS, but that did not progress to the stage of definite DCS, was given a marginal DCS classification. Each marginal case was weighted as one-tenth of a definite DCS case, because they cause a much lower level of concern for potential serious injury in human divers (12).

RESULTS

Combined human and sheep decompression dose response. The sheep and human data were each individually fit best by an LE model with two compartments. The sheep and human models required six and seven parameters, respectively, as shown in Table 3 (2nd and 3rd columns). The model fit to the combined data required seven parameters (4th column). The LR statistic for testing whether the two separate models

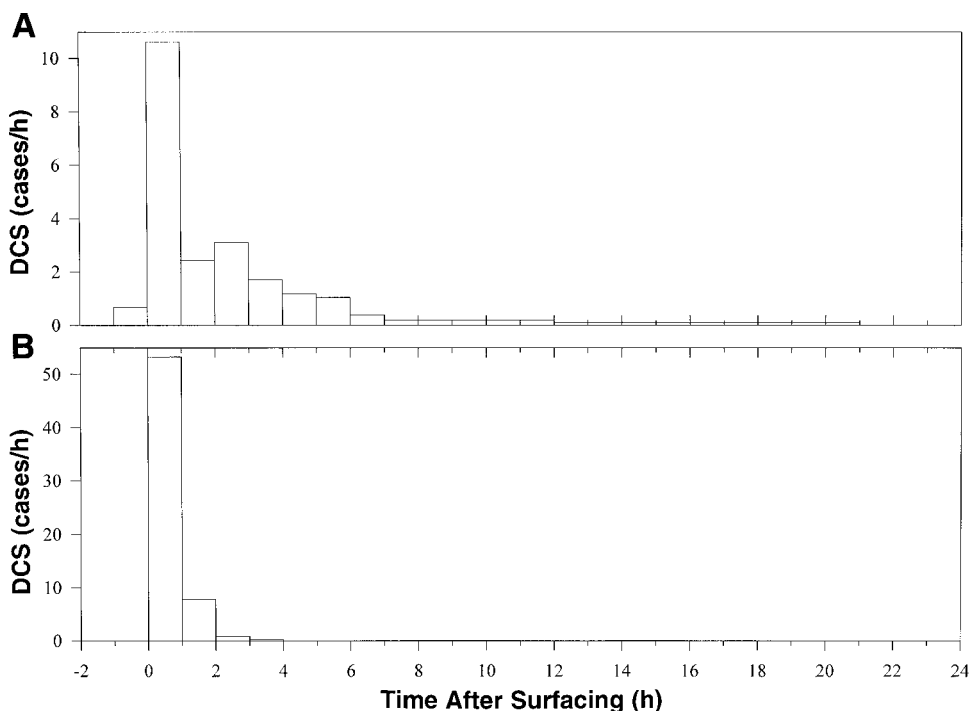


Fig. 2. Occurrence density function of time of DCS. A: human DCS; B: sheep DCS. Note all sheep DCS occur within 4 h of surfacing (B), whereas human DCS occurs as late as 24 h after return to the surface (A).

Table 2. Matching of sheep and human dives by bottom time and depth

Depth, fsw	Type	Bottom Time, min								
		30			60			240		
		Dives, no.	DCS cases, no.	Marginal cases, no.	Dives, no.	DCS cases, no.	Marginal cases, no.	Dives, no.	DCS cases, no.	Marginal cases, no.
30	Human							79	2	1
	Sheep							24	0	0
50	Human				31	2	0	62	2	7
	Sheep							54	9	5
70	Human				96	2	5			
	Sheep	8	0	0	64	1	0	2	1	0
90	Human	88	0	2						
	Sheep	24	1	1	48	5	4			
110	Human	41	2	0	62	11	5			
	Sheep	61	9	10						
130	Human	4	0	0						
	Sheep	109	31	33						

Depths are ±10 fsw. Many human dives use “equivalent air depth” for categorization. DCS, decompression sickness.

provide a better fit to the data than the combined model is given by Eq. 1

$$LR = -2[(LL_{sheep} + LL_{human}) - LL_{combined}] = -2[(259.3 + 105.9) - 376.1] = 21.8 \tag{7}$$

The LR is $> \chi^2_{(0.95, 6)} = 12.59$, so we conclude that the separate models provide a better fit to the data ($P < 0.005$). Not surprisingly, this suggests that human and sheep DCS dose responses are not identical and that some adjustment is required to obtain one from the other. To put this another way, the six “additional” estimated parameters required by the separate fits were statistically justified by the resulting improvement of the LL fit.

The parameter estimates for kinetic and response scaling are shown in the last two columns of Table 3. Each model has two compartments but requires only nine parameters. The LR statistic comparing the kinetic-scaled model with the separate models is given by Eq. 2 as

$$LR = -2[(LL_{sheep} + LL_{human}) - LL_{kinetic\ scaled}] = -2[(259.3 + 105.9) - 371.81] = 13.22 \tag{8}$$

The LR is $> \chi^2_{(0.95, 4)} = 9.49$, so we conclude that the separate models provide a better fit to the data ($P < 0.02$). This suggests that DCS responses are not similar enough in sheep and humans to be estimated from combined parameters.

Table 3. Model parameter estimates

	Sheep		Human		Combined-No Scaling		Combined-Kinetic Scaling		Combined-Response Scaling	
	1	2	1	2	1	2	1	2	1	2
τ , min	15.6 ± 5.9	113.9 ± 53.0	24.1 ± 6.7	225.6 ± 164.8	16.6 ± 2.6	173.3 ± 57.3	17.0 ± 3.0	91.1 ± 55.0	17.0 ± 3.1	133.5 ± 43.9
$\Delta\tau$, min							NS	178.3* ± 137.0		
PXO, atm	0 ± 0.1	∞	0 ± 0.2	∞	0 ± 0.1	∞	0 ± 0.1	∞	0 ± 0.1	∞
Δ PXO, atm							0.110* ± 0.115	NS		
G	-4.06 ± 0.58	-6.03 ± 0.28	-5.03 ± 0.63	-7.79 ± 0.74	-4.04 ± 0.30	-6.96 ± 0.31	-4.02 ± 0.31	-6.88 ± 0.30	-3.96 ± 0.33	-6.08 ± 0.29
Δ G									-0.540* ± 0.436	-1.76* ± 0.68
Thr, atm	1.44 ± 0.16		1.16 ± 0.22	-0.15 ± 0.08	1.44 ± 0.09	-0.096 ± 0.034	1.42 ± 0.14	-0.102 ± 0.028	1.43 ± 0.13	0 (fixed)
Δ Thr, atm									NS	-0.192* ± 0.082
LL	259.3		105.9		376.1		371.8		367.1	

Values are means ± SE. 1 and 2, compartments 1 and 2, respectively. τ , Exponential washout time constant; Δ , scaling parameter; PXO, switch from linear to exponential kinetics parameter; G, gain parameter; Thr, threshold parameter; LL, log likelihood; NS, not significant; ∞ , elimination kinetics are always exponential for compartment. *Significant scaling parameters.

The LR statistic comparing the response-scaled model with the model estimated from separate models, again using Eq. 2, is

$$LR = -2[(LL_{\text{sheep}} + LL_{\text{human}}) - LL_{\text{response scaled}}] \tag{9}$$

$$= -2[(259.3 + 105.9) - 367.1] = 3.8$$

The LR is $< \chi^2_{(0.95, 4)} = 9.49$, so we conclude that the separate models do not provide a better fit to the data ($P > 0.25$). In other words, the slight improvement in likelihood obtained by fitting two separate models is not sufficient to justify the additional four parameters required.

A first glance at the estimates of τ for the separate sheep and human models (Table 3, 2nd and 3rd columns) suggests that the sheep DCS kinetics are substantially faster than the human. However, the confidence intervals of the estimates, especially for the second human compartment, are quite large, making the parameter estimates imprecise. The combinability of the data under the response-scaled model confirms that a compromise set of kinetic parameters is equally suitable. A strong similarity is found among sheep, human, and response-scaled models in that they all require a PXO parameter in the first compartment, and the iteratively fit value of PXO is zero. The interpretation of this finding is that all data require a shift to linear kinetics in the first compartment to optimize the model fit. This finding obviously contributes to the ability to scale from the sheep to the human data.

Another indication of the goodness of fit of the response-scaled model is a comparison of the observed and predicted DCS cases shown in Table 4. By inspection, the response-scaled model predictions are quite accurate. Moreover, the response-scaled model is able to predict the human DCS cases as well as the human model, and the sheep DCS cases as well as the sheep model. Finally, a Pearson χ^2 goodness-of-fit test fails to demonstrate a difference between the observed and response-scaled model-predicted DCS counts ($P = 0.24$).

DISCUSSION

We conclude that the sheep and human data sets are combinable under the scalable LE model with jointly estimated kinetic parameters τ and PXO. Predicting human responses from sheep only requires adjustment of the response parameters. Although it is tempting to place physiological interpretations on the parameters, they are best viewed as mathematical constructs that are quasiphysiological. We present an application of

the model for predicting DCS risk on a dive not included in the calibration database that suggests the practical utility of this approach. Limitations of this study and directions for future research, including a direct test of the allometric scaling hypothesis, are discussed.

A precise physiological interpretation of the LE model parameters remains elusive. Differentiating the contribution of different physiological components, such as tissue blood flow, to the parameter values is not possible with the type of outcome data that we analyze in this work. However, the scaling parameters do tell us about differences in human and sheep DCS processes on a phenomenological level. The value of the change in gain (ΔG) for *compartment 1* (-0.540) is less negative than the value for *compartment 2* (-1.76), suggesting that the processes modeled by *compartment 2* are more important for modeling human DCS compared with sheep than are the processes represented by *compartment 1*. Similarly, the change in threshold (ΔThr) is negative in *compartment 2* but does not change in *compartment 1*, supporting the notion that human DCS depends more on the processes in *compartment 2* than on those in *compartment 1*. The emphasis on the processes represented by *compartment 2* in modeling human DCS reflects the prolonged latency of human DCS compared with sheep (Fig. 2). Only the most obvious and early DCS signs are noticeable in sheep, because they cannot complain of symptoms as can human divers. Whether the difference in response latency represents a true physiological phenomenon or simply an artifact of DCS diagnosis in sheep remains unanswered. Regardless of the underlying mechanism, for purposes of estimating DCS risk we do not need to know the physiological basis of the observation.

An application of this model is shown in Fig. 3. In this application, we test the ability of several models to predict DCS incidence of relatively high-risk human air dives (13) not included in the human or sheep calibration data set. We show the observed DCS incidence for 150-fsw no-stop air dives and the response-scaled, separate human fit, and USN93 model predictions. The error bars on the observed points are 95% binomial confidence intervals, and those for model predictions are 95% confidence intervals from propagation of errors (14). A sample of the procedure used to calculate the DCS risk shown in Fig. 3 with the use of the response-scaled model is given in the APPENDIX. We compare the predictive ability of the models by conducting the Pearson χ^2 goodness-of-fit test for the observed and model-predicted DCS outcomes. The best general model of human DCS response to date (USN93) substantially underpredicts DCS incidence in these deep no-stop dives [$P < 1 \times 10^{-6}$, $\chi^2_{(0.95, 6)}$]. The separate human and the response-scaled fits from this study both predict the DCS incidence in these dives quite well, and the predictions are both statistically indistinguishable from the observed incidence [both $P > 0.4$, $\chi^2_{(0.95, 6)}$].

This example illustrates the ability of the response-scaled model to predict outcome from high-risk human

Table 4. *Observed vs. predicted DCS*

	Observed DCS*	Sheep-only Model	Human-only Model	Response-scaled Model
Sheep DCS	62.3	64.5 ± 15.2	33.2 ± 15.0	64.8 ± 15.2
Human DCS	23.0	41.8 ± 13.0	23.1 ± 9.3	23.2 ± 10.2
Combined DCS	85.3	106.3 ± 27.0	56.3 ± 23.3	88.0 ± 17.9

Values are means ± SE of no. of occurrences. Last 3 columns are predicted values and are ±95% confidence intervals. *Marginal cases are counted as 0.1 definite cases.

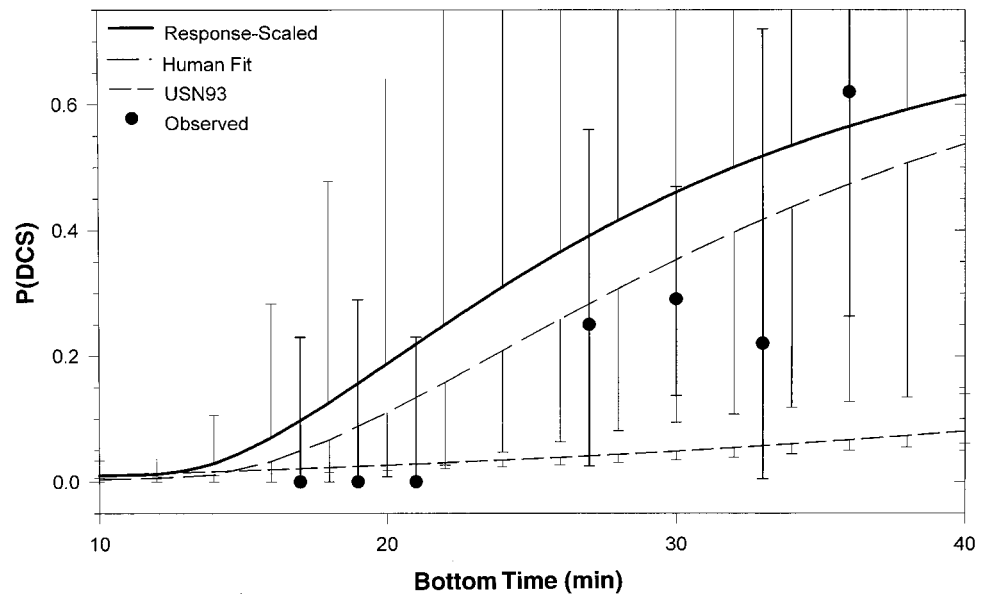


Fig. 3. Model ability to predict DCS observed incidence (●) in validation data for 150-fsw no-decompression air dive. Model USN93 substantially underpredicts DCS occurrence (short dashed line). Both human-only fit (long dashed line) and response-scaled fit (solid line) are good predictors of DCS incidence in these divers. Error bars are 95% confidence intervals on prediction for models and binomial 95% confidence interval for observed incidence.

dives not included in the calibration data set. However, it begs the question, why should the response-scaled model be used if the model fit to the human-only data predicts at least as well? The answer lies in the application of this approach to predict the risk for human dive profiles that are far beyond the range of available human data. [It should be noted that the human dives, shown in Fig. 1, were conducted more than 50 years ago (13), are unusual in the magnitude of observed DCS incidence, and would not be attempted today.] One of the limitations of an approach based on parameter estimation is that predictions are likely to become inaccurate as they are extrapolated beyond the range of the calibration data. We propose that sheep could replace humans on the extreme profiles, and the resulting response (DCS or no DCS) would be entered into the combined data set. The response-scaled model parameters would be reestimated by using this updated data set. The resulting predictions should provide reasonable estimates of the risk in humans, because of the similarity in the underlying kinetics and the adjustment made by the model for differences in DCS response. The only assumption is that the difference in response between sheep and humans represented by the response-scaled parameters remains the same for the dives in the new region. If the goal is development of a new decompression procedure for use in humans, the scaled model could provide profiles that were of acceptable risk for validation by human divers. Such an approach should make decompression table development safer and less expensive, because it would no longer be necessary to rely on human divers during the exploratory phase when DCS risk is likely to be the highest.

A limitation of this work is that it involved constructing several models and making multiple comparisons of the ability of these models to predict the observed outcome. If an adjustment for the number of comparisons is not made, then the chance of finding a falsely significant result is greater than the nominal level of

the critical value used for a single comparison (e.g., $\alpha = 0.05$). The P values obtained in our comparisons are generally much < 0.05 , making the likelihood of a false-positive study because of the multiple-comparison problem small. However, a prospective validation of this work should be conducted to fully account for the multiple-comparison issue and any other biases that may have been present, unknown to us, in the data of this study.

Ideally, prospective validation would involve both new human and sheep dives on the same profile. New human dives are costly and unlikely to be conducted simply to validate this method. A compromise is to select representative human dives already conducted and not included in this analysis and to carry out sheep dives on the same profiles. Completing the no-decompression-stop database in sheep to match the existing no-decompression dives in humans is a logical first step. This could be done by conducting air saturation dives in the 20- to 30-fsw region in which human, but not sheep data, exist. Selecting decompression stop dives that represent the full range of human data would be a next step to test whether or not these results can be reproduced with that type of dive. Dives on higher partial pressures of oxygen, dives that use helium-oxygen mixes, and dives that extend the depth and bottom time range outside of what is possible in humans might be a next step.

Additional efforts focused on extending these results to other species with smaller body mass may also prove to be useful. Our motivation to select sheep as the comparison species was based on allometric scaling of physiological rates, but we did not directly test the allometric scaling hypothesis in this study because body mass data were not available for all human subjects. The fact that human DCS risk can be accurately predicted without including body mass (12) and that human and sheep data can be combined under the response-scaled model suggests that the intraspecies

variability of body mass for sheep and humans in these data is not a controlling factor.

A direct test of the allometric-scaling hypothesis with the use of the approach introduced in this report is possible with species with greater differences in body mass, e.g., rats, pigs, goats, and sheep. An allometric approach can be incorporated into the scalable LE model by replacing the parameters used in this report with the LE parameters multiplied by body mass raised to a power. The parameter itself and the power can be estimated from the data. For example, if one wishes to test the hypothesis that τ scales allometrically, one would substitute $\tau \times (\text{body mass})^\theta$ for $(\tau + \Delta\tau)$ in the model and estimate τ and θ from the data. The procedure outlined in this manuscript for testing for combinability of different species under a scalable model by using the LR test could be followed. A better fit from a model with the use of allometrically scaled parameters would provide a means of combining data from animals without kinetic similarity. Moreover, it would provide a means of separating the role of kinetic processes from decompression responses in different species.

In conclusion, we have demonstrated the kinetic similarity of DCS after no-stop air dives in sheep and humans and have introduced a method for quantitatively adjusting for differences in decompression responses between two species. We believe this work provides a means to improve the safety and efficiency of developing new decompression procedures, to predict the risk of DCS for conditions that prohibit the use of human subjects, and to explore the differences in DCS among species of different body mass.

APPENDIX

LE Model of DCS Risk and Sample Calculations

The probability (P) of developing DCS on a given dive profile during the interval $T_2 - T_1$ is given by

$$P(\text{DCS}) = e^{-\int_{T_1}^{T_2} r dt} (1 - e^{-\int_{T_1}^{T_2} r dt}) \tag{A1}$$

where r is the risk function (15, 17). Risk is calculated only for

the 24-h period immediately after the start of decompression from the dive. Risk accumulation for the model is characterized by an instantaneous risk proportional to the sum of the risks of the two compartments (9, 12)

$$r = \sum_{i=1}^2 r_i \tag{A2}$$

$$r = \sum_{i=1}^2 e^{(G_{Ai} + \Delta G_{Hi})} \tag{A3}$$

$$\cdot \left[\frac{\text{Pti}_i + P_{\text{met}} - P_{\text{am}} - (\text{Thr}_{Ai} + \Delta \text{Thr}_{Hi})}{P_{\text{am}}} \right]$$

$$r_i \geq 0 \tag{A4}$$

where G_{Ai} is the gain factor for the sheep, ΔG_{Hi} is the additional gain for humans, Pti_i is the inert-gas burden for the i th compartment, P_{met} is a small constant contribution of metabolic gases [venous PO_2 and PCO_2 and water vapor pressure (PH_2O)], with a numerical value of 0.19 atm, P_{am} is the ambient pressure, Thr_{Ai} is an estimated threshold parameter for the i th compartment for sheep, and ΔThr_{Hi} is the additional threshold for humans. To aid the parameter estimation process, gains are parameterized in exponential form, as e^G .

Pti is a function of the following: the arterial inert-gas partial pressure [$\text{Pa}_{\text{N}_2} = (P_{\text{am}} - \text{PH}_2\text{O})(1 - \text{FI}_{\text{O}_2})$], where FI_{O_2} is the inspired fraction of O_2 ; the partial pressure of dissolved N_2 in the tissue (Ps_{N_2}); a sheep tissue time constant τ_{Ai} ; an additional time constant for humans $\Delta \tau_{Hi}$; the estimated LE crossover point PXO_{Ai} for sheep; and an additional crossover point for humans ΔPXO_{Hi} . Pti is calculated by integrating

$$\frac{d\text{Pti}_i}{dt} = \frac{1}{\tau_{Ai} + \Delta \tau_{Hi}} (\text{Pa}_{\text{N}_2} - \text{Ps}_{\text{N}_2}) \tag{A5}$$

If $\text{Pti}_i \leq (\text{PXO}_{Ai} + \Delta \text{PXO}_{Hi} + P_{\text{am}} - P_{\text{met}})$, only dissolved gas is present, Pti equals Ps_{N_2} , and gas exchange is simply exponential. If $\text{Pti}_i > (\text{PXO}_{Ai} + \Delta \text{PXO}_{Hi} + P_{\text{am}} - P_{\text{met}})$, then, in theory, a bubble is present, and excess gas comes out of solution, such that Ps_{N_2} remains constant at a level of

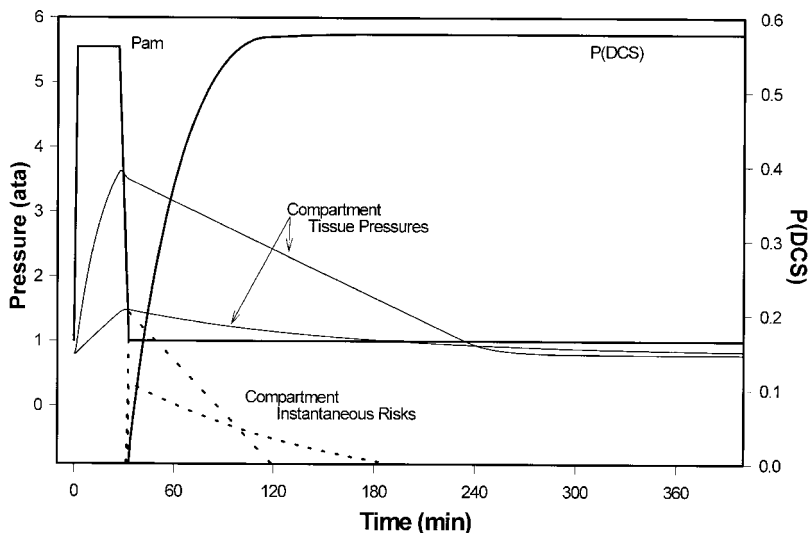
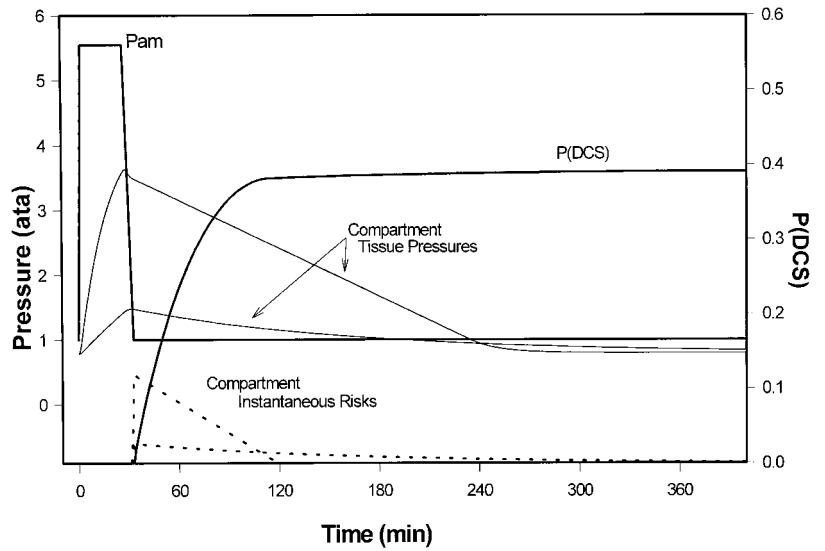


Fig. A1. Response-scaled model for sheep. Model predictions are of sheep tissue pressures, instantaneous risks, and risk accumulation [$P(\text{DCS})$] for a dive to 150 fsw for 27 min. Instantaneous risks are scaled by factors of 10 and 100 for compartments 1 and 2, respectively. P_{am} , ambient pressure.

Fig. A2. Response-scaled model for humans. Model predictions are of human tissue pressures, instantaneous risks, and risk accumulation [P(DCS)] for a dive to 150 fsw for 27 min. Instantaneous risks are scaled by factors of 10 and 100 for compartments 1 and 2, respectively.



$(PXO_{Ai} + \Delta PXO_{Hi} + Pam - P_{met})$. Thus, when depth and Pa_{N_2} are constant, exchange becomes linear with time.

Substituting the estimated parameter values for the combined-response model (Table 3, last column) into Eqs. A1–A5, we obtain for sheep (subscript S),

$$r_{1S} = (e^{-3.96}) \left[\frac{Pti_1 + 0.19 - Pam - (1.43)}{Pam} \right] \quad (A6)$$

$$\frac{dPti_1}{dt} = \frac{1}{17} (Pa_{N_2} - Ps_{N_2,1}) \quad (A7)$$

$$Ps_{N_2,1} = Pti_1 \quad \text{If } Pti_1 \leq (Pam - 0.19) \quad (A8)$$

$$r_{2S} = (e^{-6.08}) \left[\frac{Pti_2 + 0.19 - Pam - (0)}{Pam} \right] \quad (A9)$$

$$\frac{dPti_2}{dt} = \frac{1}{133.5} (Pa_{N_2} - Ps_{N_2,2}) \quad (A10)$$

$$Ps_{N_2,2} = (Pam - 0.19) \quad \text{If } Pti_2 > (Pam - 0.19) \quad (A11)$$

$$r_S = r_{1S} + r_{2S} \quad (A12)$$

and for humans (subscript H)

$$r_{1H} = (e^{-3.96 - 0.54}) \left[\frac{Pti_1 + 0.19 - Pam - (1.43)}{Pam} \right] \quad (A13)$$

$$\frac{dPti_1}{dt} = \frac{1}{17} (Pa_{N_2} - Ps_{N_2,1}) \quad (A14)$$

$$Ps_{N_2,1} = Pti_1 \quad \text{If } Pti_1 \leq (0 + Pam - 0.19) \quad (A15)$$

$$r_{2H} = (e^{-6.08 - 1.76}) \left[\frac{Pti_2 + 0.19 - Pam - (0 - 0.192)}{Pam} \right] \quad (A16)$$

$$\frac{dPti_2}{dt} = \frac{1}{133.5} (Pa_{N_2} - Ps_{N_2,2}) \quad (A17)$$

$$Ps_{N_2,2} = (Pam - 0.19) \quad \text{If } Pti_2 > (Pam - 0.19) \quad (A18)$$

$$r_H = r_{1H} + r_{2H} \quad (A19)$$

where subscripts 1 and 2 are compartments 1 and 2, respectively.

From Fig. 1, we selected 150 fsw for a 27-min dive with direct ascent to the surface. This pressure profile (Pam) can be seen in Figs. A1 and A2 for sheep and humans, respectively. Because of the complexity of the equations applied to a pressure profile, they are best solved by numerical integration. Figures A1 and A2 show the predicted inert-gas pressure in each compartment, as well as the instantaneous and integrated risks. The risk estimate from the response-scaled model for the 150 fsw for the 27-min dive with direct ascent to the surface is obtained by reading the cumulative risk P(DCS) on the right-hand y-axis in Figs. A1 (sheep) and A2 (humans).

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No animal experiments were conducted specifically for the purpose of this study. Previous animal experiments used in this analysis 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, 1985.

No experiments involving human subjects were conducted solely for the purpose of this study. Data were taken from experiments involving human subjects conducted from 1947 to 1997. These studies were reviewed and approved according to the ethics standards in place at the time the studies were conducted.

R. Ball and E. C. Parker were US Government employees and conducted this work as a part of their official duties; therefore, it cannot be copyrighted and may be copied without restriction.

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