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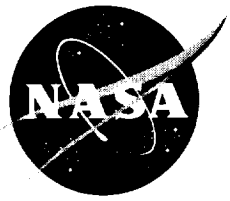

Evidence-Based Approach to the Analysis of Serious Decompression Sickness With Application to EVA Astronauts

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Acronyms and Nomenclature

CI	confidence interval
DCS	decompression sickness
EVA	extravehicular activity (space walk)
HDSD	hypobaric decompression sickness databank
ISS	international space station
LL	log likelihood
LRT	likelihood ratio test
N_2	nitrogen
O_2	oxygen
P(serious DCS)	probability of serious decompression sickness
P1	pressure before depressurization (psia)
$P1N_2$	computed nitrogen pressure in a theoretical tissue compartment (psia)
P2	pressure after depressurization (psia)
psia	pounds per square inch absolute
r_c	cumulative risk (dimensionless)
r_i	instantaneous risk (hr^{-1})
SD	standard deviation
SE	standard error
T_{alt}	planned time spent at P2 (hr)
TR	tissue ratio ($P1N_2$ / P2, unit less)

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Abstract

It is important to understand the risk of serious hypobaric decompression sickness (DCS) in order to develop procedures and treatment responses to mitigate the risk. Since it is not ethical to conduct prospective tests about serious DCS with humans, the necessary information was gathered from 73 published reports. We hypothesize that a 4-hr 100% oxygen (O_2) prebreathe results in a very low risk of serious DCS, and test this through analysis. We evaluated 258 tests containing information from 79,366 exposures in altitude chambers. Serious DCS was documented in 918 men during the tests. Serious DCS are signs and symptoms broadly classified as Type II DCS. A risk function analysis with maximum likelihood optimization was performed to identify significant explanatory variables, and to create a predictive model for the probability of serious DCS [P(serious DCS)]. Useful variables were Tissue Ratio, the planned time spent at altitude (T_{alt}), and whether or not repetitive exercise was performed at altitude. Tissue Ratio is $P1N_2$ / P2, where $P1N_2$ is calculated nitrogen (N_2) pressure in a compartment with a 180-min half-time for N_2 pressure just before ascent, and P2 is ambient pressure after ascent. A prebreathe and decompression profile Shuttle astronauts use for extravehicular activity (EVA) includes a 4-hr prebreathe with 100% O_2, an ascent to P2 = 4.3 lb per sq. in. absolute, and a T_{alt} = 6 hr. The P(serious DCS) is: 0.0014 (0.00096 - 0.00196, 95% confidence interval) with exercise and 0.00025 (0.00016 - 0.00035) without exercise. Given 100 Shuttle EVAs to date and no report of serious DCS, the true risk is less than 0.03 with 95% confidence (Binomial Theorem). It is problematic to estimate the risk of serious DCS since it appears infrequently, even if the estimate is based on thousands of altitude chamber exposures. The true risk to astronauts may lie between the extremes of the confidence intervals (0.00016 - 0.00196) since the contribution of other factors, particularly exercise, to the risk of serious DCS during EVA is unknown. A simple model that only accounts for four important variables in retrospective data is still helpful to increase our understanding about the risk of serious DCS.

Introduction

In addition to the risks of launch, and the risks to move and assemble large structures in the weightless vacuum of space during extravehicular activity (EVA), there is also a small risk of serious decompression sickness (DCS) in astronauts and cosmonauts who perform EVAs from the U.S. Space Shuttle, Russian *Mir*, and International Space Station (ISS). The decrease in ambient pressure from the 14.7 pounds per sq. in. absolute (psia) Shuttle cabin pressure (P1), to 4.3-psia space suit pressure (P2), may cause serious DCS. Serious DCS includes signs and symptoms broadly classified as Type II DCS, and would have ended the test early for a subject in an altitude chamber. Many of these symptoms would prompt a hyperbaric treatment to alleviate the symptom(s), or to reduce the likelihood of any sequela. Serious DCS is to be avoided since death sometimes follows (7,8).

Serious DCS is possible if tissue nitrogen (N_2) partial pressure is not reduced through adequate denitrogenation before the decompression, if the duration of the EVA is long, and/or if the astronaut vigorously works during the EVA. Building and maintaining the ISS will require hundreds of EVAs. Our efforts to prevent DCS have so far been successful, but the increasing number of EVAs required to build and maintain the ISS has caused us to reevaluate the likelihood of a serious case of DCS. The goal of this analysis is to accurately estimate the probability of serious DCS [P(serious DCS)] in future EVAs given information such as the denitrogenation before the decompression, the magnitude of the decompression, the exercise after the decompression, and the duration of the EVA. This is particularly challenging since the overall incidence of serious DCS is less than one percent from a survey of published reports from exposures in altitude chambers.

Estimating and controlling an event of low probability is problematic. In fact, serious DCS defies prediction. Two scenario are often invoked to describe a rare case of serious DCS: a small volume of gas is randomly transported through a Patent Foramen Ovale and then into a critical tissue, or the gas is transported in venous blood shunted past the pulmonary circulation. A bubble can also grow in a critical tissue. A practical approach to describe the risk of serious DCS is with a multivariable statistical model. Our previous survival analysis (3) estimated the risk of all DCS outcomes, with the assumption that reducing the risk of any symptom also reduces the risk of a serious symptom. Here we concentrate specifically on serious DCS. We hypothesize that a four-hr 100% oxygen (O_2) prebreathe results in a very low risk of serious DCS. We test this hypothesis through a risk function analysis of retrospective data collected from tests in altitude chambers.

Method

We needed four items to estimate our probability model for serious DCS:

a) data that contain a dichotomous (binary) response variable and one or more explanatory variables

b) a probability function, such as a risk function, that structures the model so that the outcome is a probability between zero and one

c) a model that calculates decompression dose

d) a parameter estimation algorithm on a computer that uses maximum likelihood

The risk function approach combines both the probability function and dose model into a single function without the need for additional parameters just for the probability transform. Two aims were to estimate unknown parameters that maximize the agreement between the observed serious DCS incidence and the estimated serious DCS, and to assess the goodness of fit of the particular model that best fit the data.

Data

The data are from 258 tests of exposures in altitude chambers from 1942 to 1994, and are available through the Hypobaric Decompression Sickness Databank (HDSD) (4). A test might contain a few subjects, such as a unique research project, or hundreds or thousands of subjects, such as a training flight for aviation cadets. The HDSD currently contains 456 tests, but only 258 met the selection criteria. We selected tests where males were exposed up to 8 hr in the chamber, and ascent rate was documented. The documentation of the test had to include the number of serious DCS cases that were observed, even if there were no cases. It was not necessary for the author to list all the signs and symptoms of serious DCS that were observed, but this was often done. The dichotomous response variable is Serious DCS. This category includes, but is not limited to:

- substernal disturbances (pulmonary chokes)
- involvement of the sensory, motor, and cognitive pathways of the brain and spinal cord
- sudden collapse (neurocirculatory collapse)
- unexplained weakness

Pulmonary chokes make up a substantial percentage of this category. Signs and symptoms of serious DCS not specifically attributed to arterial gas embolism would also appear in this category. Disturbances of the skin, such as rashes, mottling, paresthesia, and edema, that appeared as the only sign or symptom were not considered serious DCS in this analysis because there is no agreement on a classification of skin disturbances into either Type I or Type II DCS. Disturbances involving the skin were often placed into a separate category. Also, the 20 or so cases of death (7,8) in research and operational aviation settings since 1940 certainly qualify as more than serious DCS, and therefore are not included in this category. Table I contains a sample of signs and symptoms that were classified as serious DCS in the 73 reports. Adler (1) provides an excellent description of serious DCS collected from the literature.

The 258 tests were from 73 referenced sources, and represent 79,366 altitude exposures (see Appendix A). Twelve tests with exposures > 200 per test contributed 71,039 exposures, of which there were 544 cases of serious DCS. This subset of data is designated as "Group 1" data. These tests come from reports of military training and research activities involving many men during the years of World War II. The remaining 246 tests with exposures ≤ 200 per test contained 8,327 exposures, and documented 374 cases of serious DCS. This subset of data is designated as "Group 2" data. The non-specific selection yielded a wide variety of tests. The goal was to account for most of the variability in outcome with a multivariable model, and to identify significant explanatory variables.

TABLE I: A SAMPLE OF SIGNS AND SYMPTOMS THAT QUALIFY AS SERIOUS DCS

Substernal Disturbances	Auditory Disturbances
unproductive cough (chokes)	tinitus
dyspnea	loss of hearing
neurocirculatory collapse	loss of balance
disruption of motor, sensory, and cognitive pathways in brain and spinal cord	visual field disturbances
paralysis	diplopia
ataxia	nystagmus
dysmetria	distortion or blurring of vision
dysphagia	hemianopsia
vertigo	photophobia
dizziness	hyper or hypoesthesia
numbness	hyper or hypoalgesia
aphasia	hallucinations
amnesia	confusion
altered mood	depression
manic behavior	belligerence
disorientation	scotoma
severe headache (migraine-like)	nausea
bladder disturbances	loss of coordination
paresis in arms or legs	vomiting
cardiovascular disturbances	generalized malaise (unexplained fatigue)
syncope	hypovolemic shock
hypotension	hyperkinesias
dyskinesia	pallor
cold sweat	

There are several explanatory variables available in the HDSD: the planned time at altitude, ascent rate, whether or not repetitive exercise was performed at altitude, details about the exercise at altitude, the test altitude, and information on the denitrogenation procedure (prebreathe) before ascent, just to list a few. Table II shows summary statistics for important explanatory variables in the 258 tests. The mean, standard deviation, and range are from the 258 group-tests and not the 79,366 exposures from the tests. Since the retrospective data are from group results, the probability model for serious DCS applies prospectively to groups of men that perform similar prebreathe and decompression procedures. The variables quantify the extent of denitrogenation before the exposure ($P1N_2$), information on the transition time from site

pressure to the test altitude (ascent time, ascent rate), the test altitude (P2), the planned duration of a test (T_{alt}), and information on the exercise performed at P2 (exercise frequency, exercise type). "Exercise frequency" is the number of min of planned exercise per hr of exposure. "Exercise type" is the type of exercise performed during prebreathe and at P2, coded into eight categories as follows:

- 0 is no structured exercise during seated denitrogenation or at P2
- EXI is no repetitive exercise during seated denitrogenation, movements confined to lower body at P2
- EXII is no exercise during seated denitrogenation, movements confined to upper body at P2
- EX III is no exercise during seated denitrogenation, movements of whole body at P2
- EXIV is mild exercise while sitting during denitrogenation, movements confined to upper body while in a chair at P2
- EXV is mild exercise while sitting, supine, or head-down during denitrogenation, movements confined to upper body at P2
- EXVI is no exercise during supine or head-down denitrogenation, movements confined to upper body at P2
- EXVII is no exercise while head-down or sitting during denitrogenation, movements confined to upper body while in a chair or reclined at P2

Exercises IV through VII are complex in that exercise was or was not performed at site pressure during the prebreathe, plus body position during the prebreathe and at P2 was a variable. These data are a small subset of information, and any variability introduced into the outcome of serious DCS is accepted. There were not enough data in these categories (172 exposures with four cases of serious DCS) to justify expanding the model to account for the unique test conditions. The Results section contains how this information was evaluated. Exercises I through VII are coded as exercise = 1 when just the presence or absence of exercise at P2 was evaluated.

TABLE II. SUMMARY OF 258 DECOMPRESSION TESTS

variable	mean		SD	range
P2 (psia)	4.66		1.76	1.92 – 10.91
PIN_2* (psia)	8.60		3.04	1.52 – 12.64
T_{alt} (hr)	3.06		1.89	0.30 – 8.00
ascent time (hr)	0.156		0.140	0.017 – 0.750
ascent rate (psia / hr)	125.1		128.0	16.7 – 672.0
exercise frequency (min/hr)	14.4**		18.6	0 – 60
	additional information			
	1 (yes)	**0 (no)**	**tests**	**serious DCS**
serious DCS cases	918	78,448 (1.15%)	73	918
exercise type				
0	6,834	72,511	73	628
EXI	2,438	72,533**	80	242
EXII	794	75,907**	44	4
EXIII	3,430	78,551**	44	39
EXIV+	7	79,338**	1	0
EXV+	53	79,292**	5	2
EXVI+	92	79,253**	8	1
EXVII+	20	79,325**	2	1
exercise type plus no exercise =		79,345**	257**	917**

SD is standard deviation.

*PIN_2 ($t_{1/2}$ = 180 min) was computed using Eq. 1.

** includes one test with 21 exposures and one case of serious DCS did not document the type of exercise done at P2, so the total exposures with information on exercise type is 79,345.

The symbol + identifies 172 exposures from 16 tests with a complex exercise profile.

Table III shows specific information about Group 1 tests, plus a summary of Group 2 tests. We discuss the data as two subsets because it is instructive later when the estimated outcomes from the model are compared to the observed outcomes from Group 1 and Group 2. Compared to Group 2 tests, Group 1 tests have limited prebreathe time, limited time at altitude, and limited exercise at altitude. The ascent times and test altitudes are comparable between both sets of data. The two combined subsets complement each other by providing for a wide range of prebreathe times, exposure times, and exercise conditions while at altitude. Our conclusions are limited because the use of a multivariable model with retrospective data does not allow us to analyze the influence of all the possible variables from tests that came from different facilities at different times.

TABLE III. SUMMARY OF 12 EXTENSIVE DECOMPRESSION TESTS (GROUP 1 TESTS)

ref.	expo.	$P1N_2$* (psia)	P2 (psia)	T_{alt} (hr)	ascent time (hr)	exercise at P2	serious cases
12	223	11.60	3.00	2.0	0.156	0	11
12	204	10.95	3.00	2.0	0.156	0	4
2	343	4.48	5.00	2.5	0.042	0	0
17	245	11.31	5.22	0.3	0.105	1	0
17	379	11.31	5.22	0.3	0.105	0	0
15	9,664	11.10	3.00	1.0	0.317	0	145
15	46,683	11.20	4.36	1.0	0.350	0	327
15	4,337	11.15	4.36	1.0	0.350	0	26
15	9,738	10.70	4.36	1.0	0.350	0	19
18	434	11.51	5.95	6.0	0.025	1	0
16	585	11.51	5.95	6.0	0.033	1	1
13	204	11.03	3.00	3.0	0.217	1	12

information about the remaining 246 tests (Group 2 tests)

ref. "a"	expo.	$P1N_2$* (psia)	P2 (psia)	T_{alt} (hr)	ascent time (hr)	"b"	"c"
66	8,327					74%	374
	mean	8.50	4.67	3.10	0.150		
	SD	3.05	1.78	1.88	0.140		
	range	1.57 – 12.64	1.9 – 10.9	0.3 – 8.0	0.02 – 0.75		

*$P1N_2$ ($t_{1/2}$ = 180 min) was computed using Eq. 1
"a" 66 is the number of references for the 246 tests
"b" the percentage of 246 tests that included repetitive exercise at P2
"c" the number of serious DCS cases in the 246 tests

Denitrogenation and the 180-Minute Half-Time Compartment

The tissue N_2 partial pressure ($P1N_2$) is an important variable in any model about DCS. Prebreathing 100% O_2 or O_2-enriched mixtures before a hypobaric decompression is an effective and often-used technique to prevent DCS. Therefore, it is necessary to account for the use of O_2-enriched mixtures before decompression using Eq. 1. Equation 1 defines how $P1N_2$ is calculated; it approximates a more complex process of dissolved N_2 kinetics in living tissue. Following a step-change in N_2 partial pressure in the breathing medium, such as during a switch

from ambient air to a mask connected to 100% O_2, the N_2 partial pressure that is reached in a designated tissue compartment after a specific time is:

$$P1N_2 = P_0 + (P_a - P_0) * (1 - e^{-\kappa t}), \qquad \text{Eq. 1}$$

where $P1N_2$ = the N_2 partial pressure in the tissue after t min, P_0 = initial N_2 partial pressure in the compartment, P_a = ambient N_2 partial pressure in breathing medium, e = base of natural logarithm, and t = time at the new P_a in minutes. The tissue rate constant κ is defined as 0.693 / $t_{1/2}$, where $t_{1/2}$ is one of six tissue N_2 partial pressure half-times: 120, 180, 240, 300, 360, or 420 min in this analysis. The initial, equilibrium N_2 pressure (P_0) in the tissue at sea level is taken as 11.6 psia instead of an average alveolar N_2 pressure of 11.0 psia. The use of dry-gas, ambient N_2 pressure as equilibrium tissue N_2 pressure (P_0), and as the N_2 pressure in the breathing mixture (P_a), makes the application of Eq. 1 simple.

Figure 1 shows a vertical and horizontal array of 258 circles, which represent a total of 79,366 exposures by men in altitude chambers, on a P2 vs. $P1N_2$ plot. The area of each circle represents the incidence of serious DCS symptoms in a test. The largest circle is 44.8% incidence from a test with 29 exposures and the 193 smallest circles are tests with no cases of serious DCS. Consider the vertical array of circles located between about 10.0 and 11.6 psia on the x-axis. These circles represent results from an ascent to P2 without the benefit of significant denitrogenation. Notice the area of the circles appears to increase as P2 decreases for a constant $P1N_2$, calculated using Eq. 1 with $t_{1/2}$ = 180 min. Consider also the horizontal array of circles at about 4.3 psia on the y-axis. These circles represent results from tests at about 4.3 psia, but which experienced a wide range of denitrogenation. Notice the area of the circles also increases as $P1N_2$ increases with P2 constant at about 4.3 psia. There were only six tests (24 cases of serious DCS in 261 exposures) in the region of the graph below 2.5 psia (41,500 ft) where mild hypoxia is expected even when 100% O_2 is delivered under positive pressure in the breathing mask. Signs and symptoms of mild hypoxia could have been misdiagnosed as serious DCS, or could have exacerbated some cases of serious DCS.

This figures does not identify the duration of each test or whether exercise was performed during the test. These two variables also influence the likelihood of serious DCS, and partially explain why serious DCS appears in regions where serious DCS might not be expected. Also, small circles in the right corner could be from tests where the exposure time was short, or there was no exercise, or both. Finally, the observed DCS incidence, and therefore the area of each circle, is also influenced by the number of subjects in a test, since a larger sample size is expected to provide a better estimate of the incidence. The multivariable risk function in the next section accounts for more than the two variables seen in this two-dimensional figure.

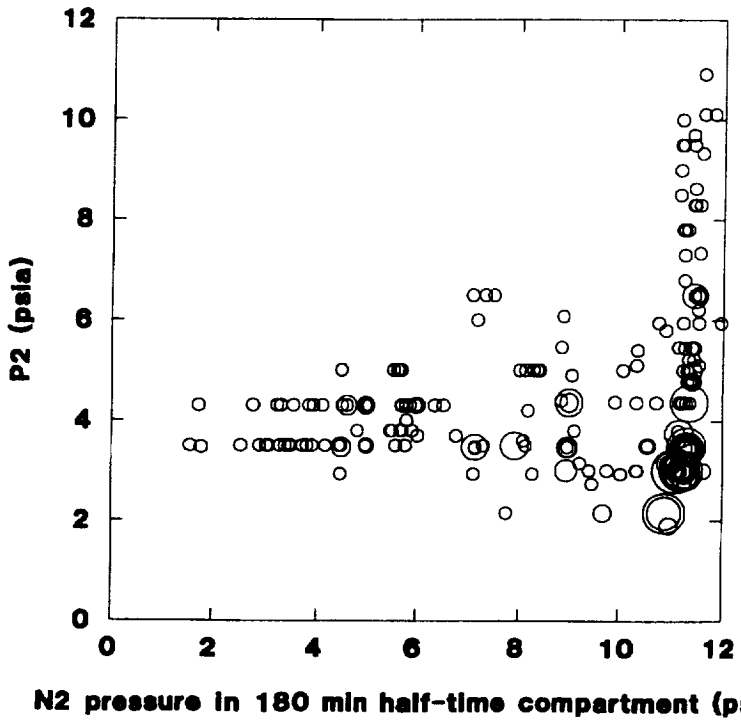

Fig. 1. The circles are 258 tests on a P2 vs. $P1N_2$ plot. The P1N2 for each test was calculated using Eq. 1 with $t_{1/2}$ = 180 min to account for denitrogenation before ascent to P2. The area of each circle represents the incidence of serious DCS observed during the test. Most of the large circles appear in the lower right corner where limited denitrogenation occurred before ascent and where the test altitudes were between 2.0 and 5.0 psia.

Probability Function: Risk Function Model

We modify and parameterize a risk function published by Van Liew (18,19) for the analysis presented here. The instantaneous risk (r_i) is a function of time and explanatory variables associated with serious DCS. The relationship between r_i and time t may be very simple (a constant, for example) or a more complex expression such as $r_i = t * e^{-\beta t}$. The particular risk function chosen for the present analysis is:

$$r_i = \chi * \left(\frac{P1N_2}{P2} \right)^{\alpha} * [1 + EXER * \varepsilon] * (t * e^{-\beta t}) \qquad \text{Eq. 2}$$

where α, β, χ, and ε are unknown parameters to be estimated from data, and $P1N_2$ (psia), P2 (psia), EXER, and T_{alt} (hr) are the four variables associated with this four-parameter continuous model. Equation 2 combines both mechanistic and empirical components. The change in r_i with respect to time is suggested from observations on the rate at which DCS appears (3,5,18). We believe the ratio of $P1N_2$ to P2 to a power α links an evolved volume of gas to the perception of

pain better than the ratio alone, and better than the difference in pressure alone (5). Finally, the contributions from the type, intensity, and duration of exercise while at altitude to the risk of serious DCS are not known. Our simple approach is to estimate a "weight" term ε to account for the contribution of any repetitive exercise while at altitude to the risk of serious DCS.

For a test of duration T_{alt}, the integral of r_i with respect to time gives the cumulative risk (r_c). That is,

$$r_c = \int_0^{T_{alt}} r_i(t)dt . \qquad \text{Eq. 3}$$

Using r_i given by Eq. 2 in Eq. 3, we obtain the following expression for the estimated cumulative risk:

$$r_c = \chi * \left(\frac{P1N_2}{P2}\right)^{\alpha} * [1 + EXER * \varepsilon] * \frac{1-(1+\beta T_{alt}) * e^{-\beta T_{alt}}}{\beta^2} \qquad \text{Eq. 4}$$

In terms of r_c, the probability of serious DCS sometime before the end of the test is:

$$P(\text{serious DCS}) = 1 - e^{-r_c} \qquad \text{Eq. 5}$$

where e^{-r_c} is P(no serious DCS). Notice that P(serious DCS) is zero if the cumulative risk is zero and approaches one as the risk increases. From Eq. 5, it can be seen that r_c = - ln[1 - P(serious DCS)], where ln is natural log. Notice that r_c is dimensionless. The derivative of r_c with respect to time is r_i, so r_i = d(- ln[1 - P(serious DCS)]) / dt, or the rate in a finite interval of time at which serious DCS appears in the data set.

This analysis was limited because the specific time of serious DCS (failure time) reported for each subject and the actual duration of some exposures that were shorter than the planned duration were not available. Recall that T_{alt} is the duration of the planned test. Serious DCS occurred during the interval from the start of the test on arriving at P2 to the end of the planned test. When serious DCS occurred, the subject was removed (locked out) from the chamber, and the test was allowed to proceed, or the entire test was stopped, thus censoring the failure time for those subjects who may have gone on to develop serious DCS. A subject with mild pain-only symptoms may have been allowed to continue the test. However, a subject with intense pain-only symptoms, but not serious DCS, would have been removed from the chamber. It is not known if that subject would have progressed to a serious symptom. These complexities mean that the model likely underestimates the true risk of serious DCS since an unidentified subset of men without serious DCS were removed from the tests early for various reasons. These unidentifiable cases were still assigned the T_{alt} of the test and coded as "0" for not having

serious DCS. Those subjects with serious DCS were coded as "1", and also assigned the T_{alt} of the test, no matter when the sign or symptom appeared.

Parameter Optimization and Goodness of Fit

The SYSTAT (ver. 5.03) Nonlin module (21) was used to estimate unknown parameters in the model, with optimization employing the Quasi-Newton algorithm. The P(serious DCS) was computed using Eq. 5 and iteratively adjusted using data to optimize the model parameters through the likelihood function. Maximum likelihood optimization in our application entails minimization of the summed positive log likelihood (LL) number, and the details are covered elsewhere (2, 20, 21), and in Appendix B. The best-fit continuous model from this statistical approach does not necessarily mean that there is a good fit of the model to the data. Goodness of fit of the best-fit model provides information about how confident one can be in the estimate of serious DCS.

One method to assess goodness of fit is to compare the LL numbers for three models: the null model, the discontinuous model, and the best-fit continuous model, using the Likelihood Ratio Test (LRT) (10). The LRT is used to compare two models that differ by at least one parameter. It can determine if the best-fit continuous model is statistically better than the other two models: the null and discontinuous (20). The test involves comparing the LLs of two models, the restricted and unrestricted, fitted to the same data set. A restricted model can contain a single constant, the null model. The null model is a constant-probability model based on the mean serious DCS incidence of all the individuals in the data set. A large LL results with the null model since no explanatory variables are used to "explain" the outcome. In the same data set, a small LL from a discontinuous, or saturated, model is defined as the best, or perfect LL based on the definition that the DCS incidence in each group result is the true DCS incidence. The discontinuous model has as many degrees of freedom as there are tests, 258 in this case. The best-fit continuous model based on theory would not perfectly predict the observed DCS incidence in all tests, so the summed LL would always exceed the summed LL for the discontinuous model. Equation 6 calculates the LL for the discontinuous model:

$$LL = \sum_{i=1}^{n} \ln \left[(1 - c_i)^{(\text{no serious dcs}_i)} * (c_i)^{(\text{serious dcs}_i)} \right], \qquad \text{Eq.6}$$

where "n" is the number of groups, ln is natural log, c_i is the fraction of subjects with serious DCS in group "i", (no serious dcs_i) is the number of subjects without serious DCS in group "i", and (serious dcs_i) is the number of subjects with serious DCS in group "i".

The restricted model always has fewer degrees of freedom than the unrestricted model. The idea is to test if the addition of one or more parameters to the unrestricted model is better than the null

model by testing the hypothesis that the additional parameter has a zero value. The value of the Likelihood Ratio statistic is calculated as two times the difference in the LL between the unrestricted and restricted models. The statistic follows an approximate χ^2 distribution with degrees of freedom equal to the difference in the degrees of freedom between the unrestricted and restricted models. The value of the statistic and the degrees of freedom are entered into a χ^2 table to find the corresponding p-value. A p-value < 0.05 indicates that the null hypothesis should be rejected, i.e., that the additional parameter is not zero. In addition to determining if the best-fit continuous model is statistically superior to the null or discontinuous models with the LRT, it is possible to approximate a goodness of fit of the continuous model by comparing the LL of the model to the LLs of the null and discontinuous models. The percent improvement over the null model is calculated as: [(LL null model - LL continuous model) / (LL null model - LL discontinuous model)].

Results

Best-Fit Model

Table IV shows the four parameters, parameter estimates, standard errors, T-ratios, and correlation matrix for the best-fit model selected from a list of several competing models (not shown). All four fitted parameters were significant enough to remain in the model. The best-fit model accords with observations in that limited prebreathe before ascent, or ascent to a high altitude, or a lengthy exposure time, or exercise at altitude results in a greater risk of serious DCS. Six half-times from 120 to 420 min at 60-min intervals were evaluated once a promising model was developed. The LL for the best model improved by eight units on going from a 360- to a 180-min half-time compartment. A faster half-time compartment amplifies small differences in prebreathe times, thus indicating that prebreathe time is an important explanatory variable.

Modifying the model with inclusion of information on specific exercise type and ascent rate did not improve the fit; the additional parameters were not statistically significant. Also, fitting several models without the data from 16 tests with complex exercise profiles (172 exposures with four cases of serious DCS (see Table II) did not improve the overall goodness of fit. There was no systematic change in the parameter estimates or the standard error of the estimates in the best-fit model. The largest change was a 6% decrease in the value of the scale term χ. The probability estimates for the model based on 79,194 exposures for various simulations (not shown) were within the 95% confidence intervals of the best-fit model based on 79,366 exposures.

TABLE IV. PARAMETER ESTIMATES OF FOUR-PARAMETER MODEL

Parameter	Estimate	Asymptotic SE	T-ratio
χ (scale)	0.000613	0.000133	4.60
β (rate)	1.794	0.219	8.19
α (power)	4.267	0.142	30.0
ε (weight)	4.752	0.548	8.67

SE is standard error, T - ratio is the ratio of the estimate to the SE of the estimate, and an absolute value > 1.96 indicates that the p - value for the estimate is < 0.05 for the test that the true parameter value is zero.

ASYMPTOTIC CORRELATION MATRIX

	χ	β	α	ε
χ	1.000			
β	0.660	1.000		
α	-0.781	-0.085	1.000	
ε	0.408	0.663	-0.121	1.000

Other candidate models with various combinations of the parameters and the four explanatory variables in the context of Eq. 2 were tried. Expressing N_2 supersaturation as a difference in pressure [$P1N_2(t_{1/2})$ - P2] was not as good as when supersaturation was expressed as a ratio of pressures [$P1N_2(t_{1/2})$ / P2]. Adding a power term α to the pressure ratio dramatically improved the model (LL = 4273 with α compared to 4556 without α), as was the case in a previous effort (5). The addition of the scale parameter χ was statistically justified. The LL was 4314 without the parameter and improved by 41 units when included in the model ($p < 0.001$ from the LRT). Also, the correlation matrix in Table IV shows that this parameter is not highly correlated with the three other parameters, another indication that it is not redundant and contributed to the description of the data.

The LL number for the four-parameter continuous model was 4273, compared to 5006 for the null model, and 1191 for the discontinuous model. The continuous model was statistically better than the null model, but not as good as the discontinuous model, in both cases $p < 0.0001$ from the LRT. The null model estimated the best risk of serious DCS for any exposure to be 0.0115, the mean incidence in the data set, with narrow 95% confidence interval of 0.0108 to 0.0123. The improvement of the continuous model over the null model was about 19%.

Two simpler expressions for r_i were also evaluated, $r_i = \gamma$, a constant, and $r_i = t$. For $r_i = \gamma$, integration with respect to t gives $r_c = \gamma T_{alt}$, which is a straight line passing through the

origin with slope = γ. This r_c with the three parameters (χ, α, ε) gave a LL of 4306. For $r_i = t$, $r_c = T_{alt}^{\ 2} / 2$, so there was no additional term to parameterize. This r_c, also with the three parameters, gave a LL of 4478. Neither model was statistically superior to the r_i defined in Eq. 2 (LL = 4273), which also included a fourth fitted parameter, β. We also evaluated the standard logistic regression model in the Logit module of SYSTAT (21). Given the same four variables and four parameters, the LL was worse at 4333 (results not shown). We interpret this as evidence that our efforts to understand serious DCS in mechanistic terms have advantage over a non-mechanistic approach. We conclude that these data required a risk function that first increases and then decreases in time, just as seen in two other models that describe the P(DCS) (3) and the P(forced descent DCS) (18,19).

Threshold for Serious DCS

The model describes the data and the data indicate that even at low decompression stress (low values of r_c), there is a risk of serious DCS (Appendix C). Figure 2 shows a comparison of the observed group incidence from 257 tests with the computed r_c from Eq. 4 to facilitate a discussion about a "threshold" for serious DCS over the entire range of the data. A threshold means that a minimum decompression stress must be exceeded before an outcome is observed. One data point at $r_c = 0.588$, with an observed incidence of serious DCS of 27% from a test with 29 men, is excluded from Fig. 2 so that data from the remaining 257 tests could be clearly displayed. Since r_c is a function of four variables, it is possible to have a high or low value depending on the magnitude of the variables. Notice that the calculated P(serious DCS), the solid line from Eq. 5, is nearly linear, and passes through the origin. But it is not possible on Fig. 2 to see information at very low values of r_c, so the examination of threshold is continued by evaluating data at very low r_c.

Figure 3 shows the observed group incidence of serious DCS over a range of very low r_c values. There were just six cases of serious DCS in 3,687 exposures (109 tests) with $r_c \leq 0.0045$. The lowest value of r_c with a case of serious DCS was 0.00145, and was from a test with ten males with a single case of serious DCS. There were 2,178 exposures in 56 tests below this value of r_c where no case was reported. A 4-hr prebreathe followed by a 6-hr exposure to 4.3 psia that does not include exercise provides an $r_c = 0.000254$, well below the value of r_c where a case of serious DCS was reported. If exercise is included in the exposure, then $r_c = 0.00146$. Finally, in Group 1 tests, the lowest value of r_c was 0.00469 in 9,738 exposures associated with 19 cases of serious DCS. Even though the model extrapolates P(serious DCS) to $r_c = 0$ (curve on Fig. 3), there is an interval between zero and 0.00145 where no case has been reported.

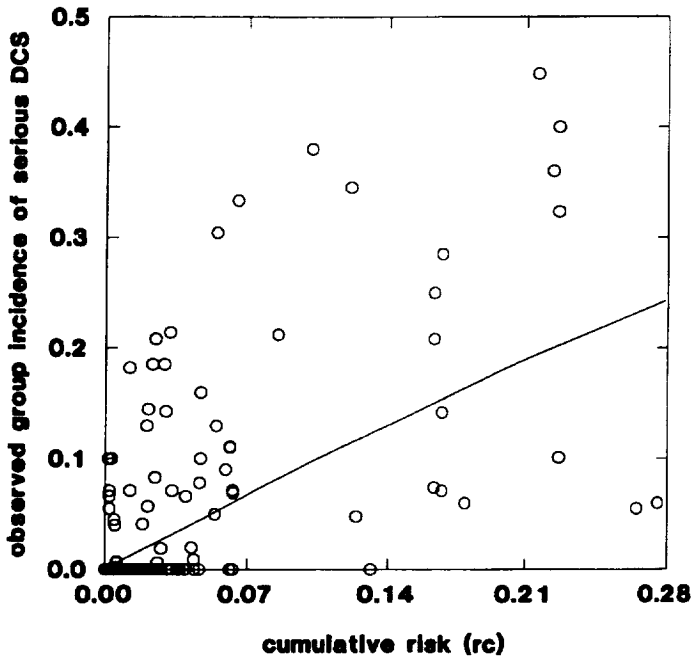

Fig. 2. Observed group incidence of serious DCS in 257 tests versus the computed r_c from Eq. 4. Notice at $r_c < 0.07$ that there is a wide range of incidence. Due to the range of the x-axis, a "threshold" interval for serious DCS cannot be seen. The solid line is the calculated P(serious DCS) using Eq. 5, which is approximately linear because $1 - e^{-r_c} \approx r_c$ for small values of r_c.

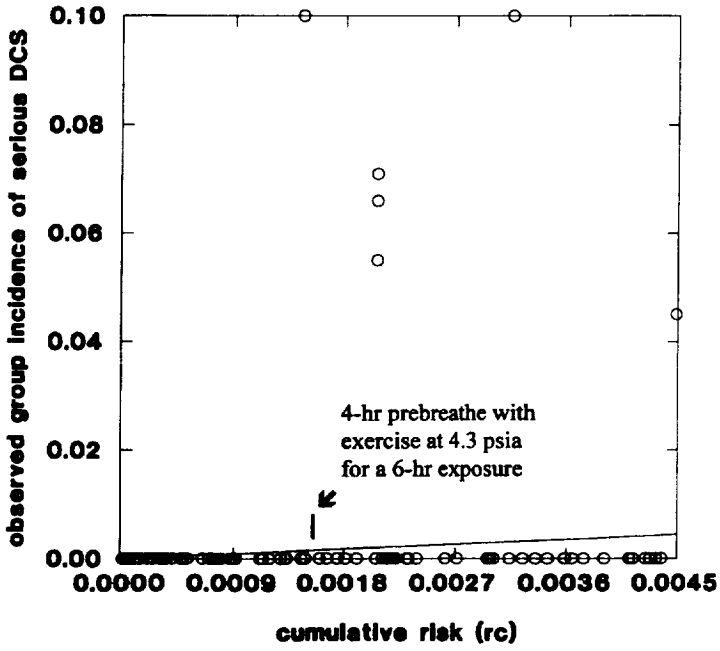

Fig. 3. Observed group incidence of serious DCS in 109 tests at very low r_c versus the computed r_c from Eq. 4. In the interval $r_c \leq 0.0045$ there were only six cases of serious DCS in 3,687 exposures from 109 tests, and no cases in the interval $r_c \leq 0.00145$. This is an interval where the combinations of prebreathe and decompression procedures can be adjusted such that no case of serious DCS is expected.

Model Simulations Relevant to EVA Astronauts

Figures 4, 5, 6, 7, and 8 pertain to hypothetical scenarios where the values of the explanatory variables are in the range of the data, and in a range of interest to astronauts who perform EVAs. The scenarios reflect lengthy prebreathes, with ascent to 4.3 psia, exposure times up to 6 hr (the length of a typical EVA), and with or without repetitive exercise being performed while at 4.3 psia. Figure 4 shows r_i changing through time at altitude for two prebreathes (3 – 4 hr), a test altitude of 4.3 psia, and with or without repetitive exercise at altitude. The rate at which serious cases of DCS occur in these simulations as a function of time at altitude approaches zero after about 4 hr. Figure 5 shows r_c as it increases through time at altitude for the same conditions as in Fig. 4. The accumulation of additional risk is minimal after about 3 hr at altitude.

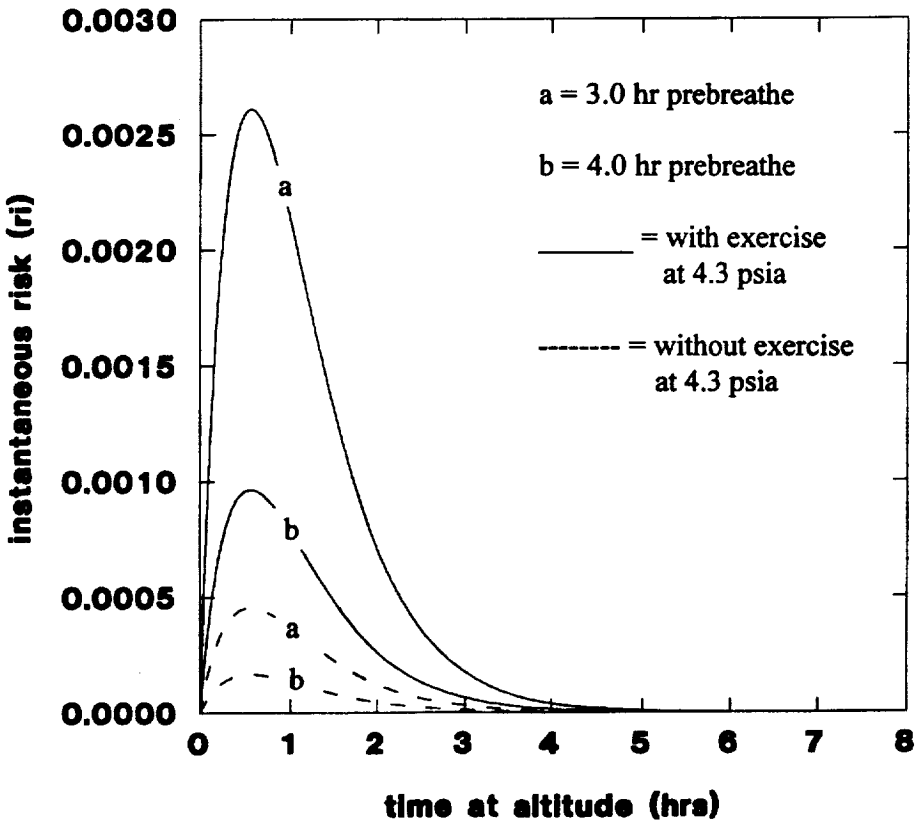

Fig. 4. Results of simulations to demonstrate changes in r_i from Eq. 2. The rise and fall of r_i over a short interval of time is also observed in other categories of DCS outcomes.

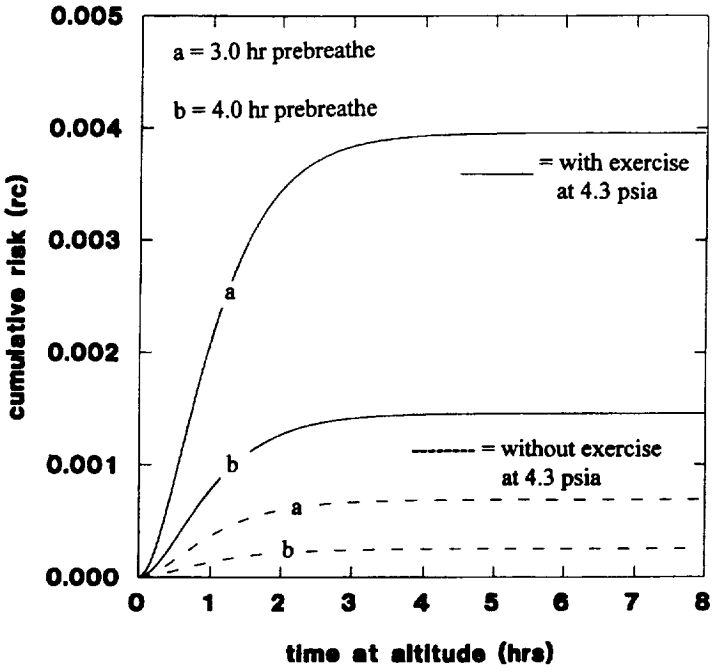

Fig. 5. Results of simulations to demonstrate changes in r_c from Eq. 4. There is a limited accumulation of additional risk after about 3 hr.

Benefits From Even Limited Prebreathe

Figure 6 shows the P(serious DCS) from Eq. 5 as a function of time at altitude in scenarios that include exercise at 4.3 psia with no prebreathe before ascent, or prebreathes of 0.5, 1.0, 2.0, or 3.0 hr. Notice the significant reduction in the P(serious DCS) with a limited prebreathe of 0.5 hr of O_2 compared to the case with no prebreathe. There is about a 40% reduction in risk at the sixth hr after a 0.5-hr prebreathe compared to no prebreathe [(0.073 - 0.045) / 0.073 = 0.4], and about a 60% reduction in risk after a 1-hr prebreathe [(0.073 - 0.028 / 0.073 = 0.6]. Figure 7 shows the P(serious DCS) as a function of time at altitude in simulations without exercise at 4.3 psia with no prebreathe before ascent, or prebreathes of 0.5, 1.0, 2.0, or 3.0 hr. The y-axis scale is expanded compared to Fig. 6 to clearly show the lower risk when exercise is not performed at altitude. Notice that there is about a fivefold decrease in the P(serious DCS) for each case in this figure compared to the cases in Fig. 6. It is important to prebreathe 100% O_2, at least for 30 min, before ascent and to limit exercise while at altitude to avoid serious DCS.

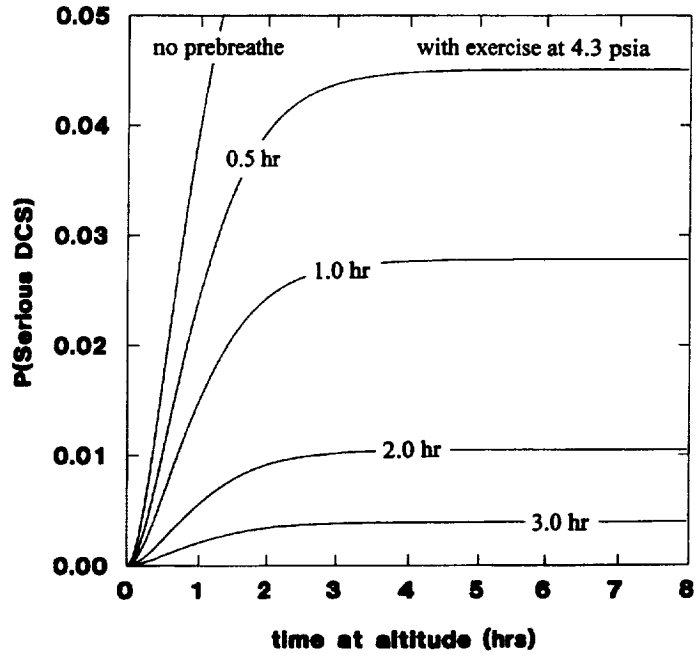

Fig. 6. The contribution of prebreathe duration (indicated by labels) toward reducing risk in astronauts who exercise at P2. The probability curves are specific to an exposure to 4.3 psia. The ratio of $P1N_2$ to P2 for the 180-min half-time compartment with no prebreathe before ascent is 2.69, and decreases by half to 1.34 after a 3-hr prebreathe.

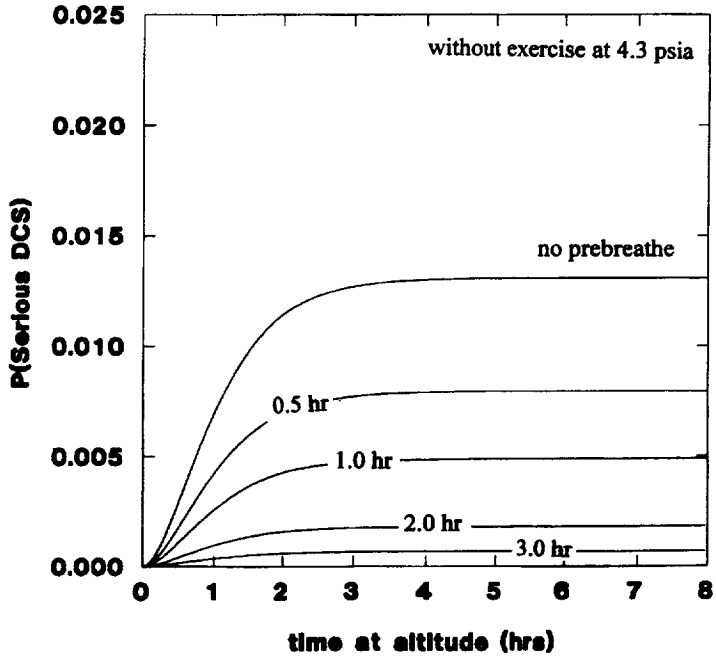

Fig. 7. The contribution of prebreathe duration (indicated by labels) and inactivity toward reducing risk. The shapes, but not the magnitudes, of the probability curves are the same as in Fig. 5 since the contribution of exercise toward serious DCS is a constant in the model. Note that the y-axis scale is twice as large as in that of Fig. 6.

Best Estimate for Serious DCS in EVA Astronauts

Figure 8 shows the P(serious DCS) as a function of time at altitude after a 4-hr prebreathe in scenarios with and without exercise at 4.3 psia. Notice in this figure, as well as in Figs. 6 and 7, that the P(serious DCS) increases rapidly over the first 3 hr, and then increases only slightly for the remainder of the altitude exposure. The model reflects the observation in the data that most signs and symptoms of serious DCS occur early in the altitude exposure, a period in which to be vigilant. The examples shown in Figs. 4 - 8 are specific for a prebreathe procedure available to astronauts who perform EVAs. Unfortunately, astronauts' actual exercise during EVA and the denitrogenation associated with adaptation to microgravity is not well understood. Therefore, our best estimate of risk for serious DCS is between the extremes of the 95% confidence intervals at the sixth hr of altitude exposure, between 0.00016 (0.016%) and 0.00196 (0.196%). There has not been a case of serious DCS (or any DCS) in the previous 100 Shuttle EVAs. Using the binomial distribution, we can say that the one-sided 95% upper bound on the risk of serious DCS is no greater than 0.03, or about 15 times greater than our worst-case estimate of 0.00196 for a "typical" Shuttle EVA. By the same logic, it would require 1660 EVAs without serious DCS to have confidence in our worst-case estimate.

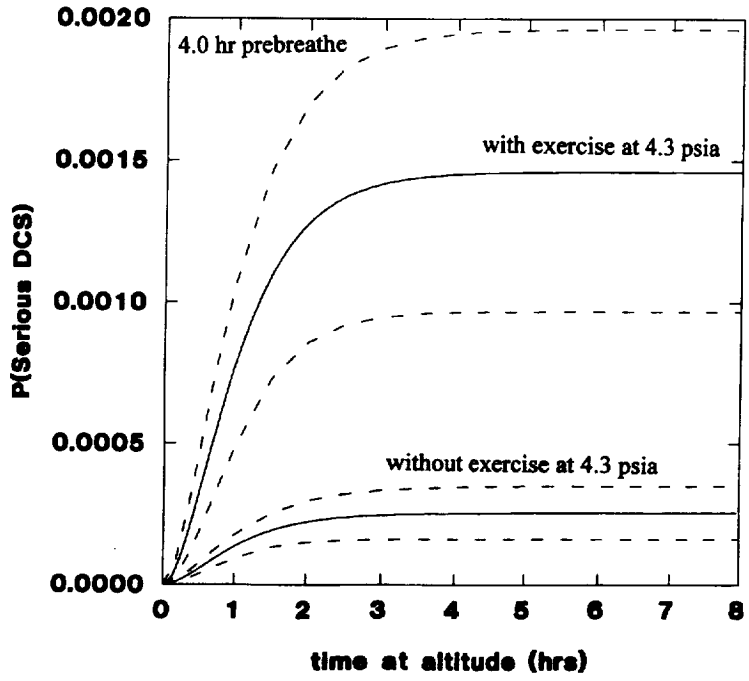

Fig. 8. A simulation to show the P(serious DCS) specific for conditions that astronauts may encounter during EVAs from the ISS. The wide confidence intervals for estimates that include exercise reflect the limited understanding of how exercise influences the likelihood of serious DCS, and also the limited amount of data that included information about exercise. The 95% confidence intervals were calculated based on a propagation of errors formula (11). The intervals provide a defined range for the estimate, but do not establish the accuracy of the estimate.

Qualitative Assessment of Goodness of Fit

Equation 4 is the expression for decompression dose that was the best-fit of various candidate models regardless of the strength of the relationship between the dependent and independent variables. Goodness of fit, after obtaining the model with the best fit, is a measure or impression of agreement between the estimated outcome and the observed outcome. Without a goodness-of-fit assessment it is possible to be unjustifiably confident in an estimate of P(serious DCS) as a function of the explanatory variables. Table V shows a comparison between the observed and estimated cases of serious DCS from Group 1 tests. In about half of the tests the model performed well. But in several large tests, the model either over- or underestimated the observed cases. Overall, the model overestimated 84 out of 544 observed cases of serious DCS.

TABLE V: COMPARISON OF OBSERVED AND ESTIMATED SERIOUS DCS IN 12 TESTS (GROUP 1 TESTS)

Ref.	Exp.	serious cases observed	serious cases estimated	estimated - observed
12	223	11	11.5	-0.5
12	204	4	8.3	4.3
2	343	0	0.04	0.04
17	245	0	0.7	0.7
17	379	0	0.2	0.2
15	9,664	145	205	60
15	46,683	327	266	-61
15	4,337	26	24	-2
15	9,738	19	45	26
18	434	0	8.0	8
16	585	0	10	10
13	204	12	49	37
totals	71,039	544	628	overestimated 84 cases

Figures 9 and 10 graphically show how well Eq. 5 described the data. Figure 9 shows the observed incidence for Group 2 tests compared to the estimated incidence from the model. The area of each circle is proportional to the number of subjects in the test. The smallest circle indicates a test with two subjects while the largest indicates a test with 195 subjects. There were 374 cases of serious DCS in 8,327 exposures in these 246 tests. Tests below the identity line were underestimated, and those above the line were overestimated. Although difficult to see due

to the scales used, tests along a vertical line at zero observed group incidence may at first seem to indicate that the model severely overestimates the risk of serious DCS in these tests. However, tests along the horizontal line at zero observed group incidence on Fig. 2 with $r_c < 0.07$ are associated with other tests in that range that show group incidence up to 33%. The estimated risk from the model does balance the variability seen in these data at low r_c, so the estimated incidence seen along the y-axis is reasonable even when the observed incidence is zero for several tests. The visual goodness of fit based on group incidence is limited because the precision of group incidence is greatly influenced by the number of subjects in a group.

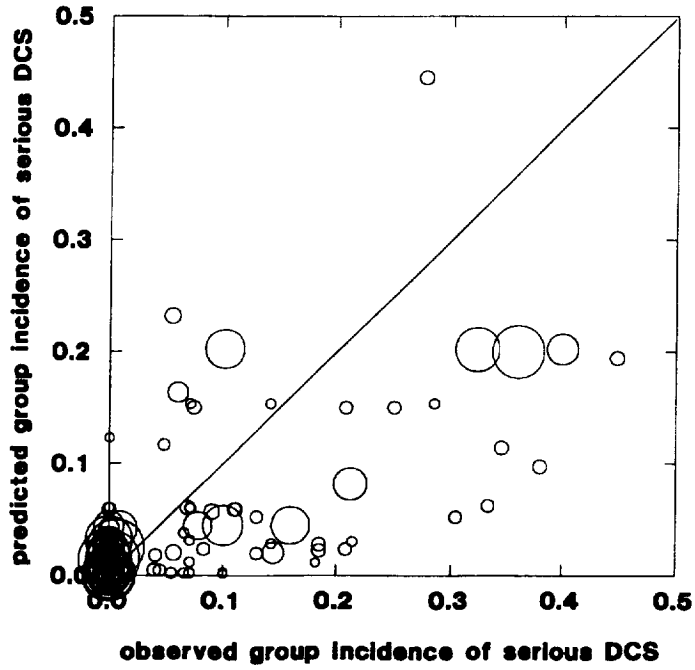

Fig. 9. A comparison of the estimated to the observed serious DCS in Group 2 tests. The area of a circle is proportional to the number of men in a test. At this scale, the model appears to underestimate the observed incidence as evident by the scatter of tests below the identity line. Looking at the data from zero to 10% on an expanded scale, the model appears to overestimate the observed incidence. The model does not systematically over- or underestimate the observed incidence over the entire range of the data. The cluster of circles near the origin represents 191 tests with serious DCS < 0.03.

Figure 10 shows the observed incidence compared to estimated incidence for Group 1 tests. Data from tests with large number of men contribute more to the model, so larger circles are located nearer to the identity line in Fig. 10 compared to Fig. 9. There were 544 cases of serious DCS in 71,039 exposures in these 12 tests. Except for one test far above the identity line, the model reasonably estimated the observed group incidence. This is not surprising since the parameters for the model are influenced by the large number of exposures contained in these tests. The position of all the circles on Figs. 9 and 10 gives an impression of a reasonable fit of Eq. 5, given the simple formulation of the model, the realization that random variability in the

outcome will not be completely accounted for, and the limitation of these figures to provide an assessment of goodness of fit.

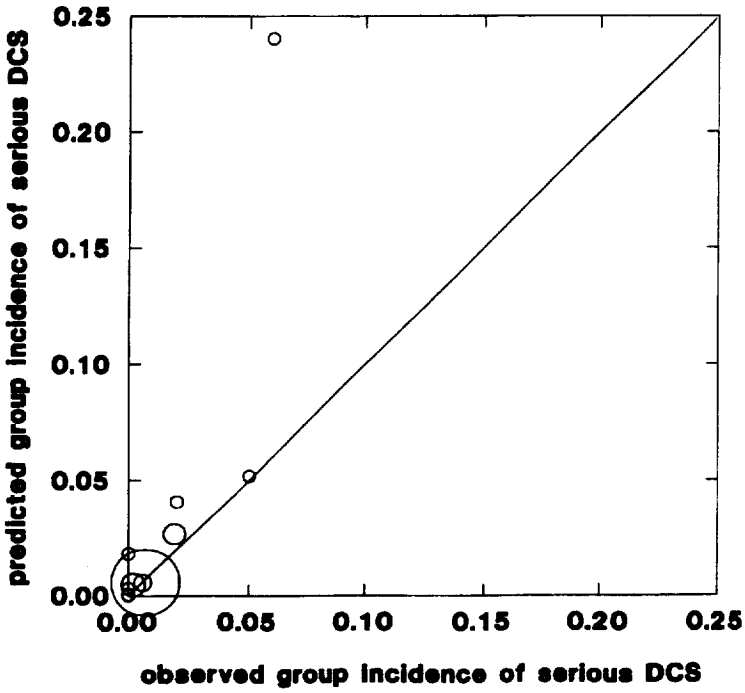

Fig. 10. A comparison of the estimated to the observed serious DCS in Group 1 tests. The area of a circle is proportional to the number of men in a test, but not the same proportionality as in Fig. 9. Observed and estimated appear in better agreement than in Fig. 9, which is expected due to the larger sample size and greater influence on the model parameters.

We continue to evaluate goodness of fit by expanding the observed group incidence along the y-axis from zero to 5%. Figure 11 shows positive estimated incidence for tests along a vertical line at zero observed group incidence. This indicates that the model overestimates the risk of serious DCS in these tests. However, the tests along a horizontal line of zero observed group incidence on Fig. 2 with $r_c < 0.07$ are associated with other tests in that range that show group incidence up to about 33%. Figure 3 shows more clearly the P(serious DCS) through a region where the group incidence was mostly zero, at very low $r_c \leq 0.0045$. The estimated risk from the model does balance the variability seen in the data at low r_c. The overestimation at very low r_c is partially due to fitting the model through a wide range of r_c so that extrapolating the model to very low r_c is associated with some risk, even in a region where no cases were observed. This explains the appearance of the circles along the y-axis at a zero observed group incidence.

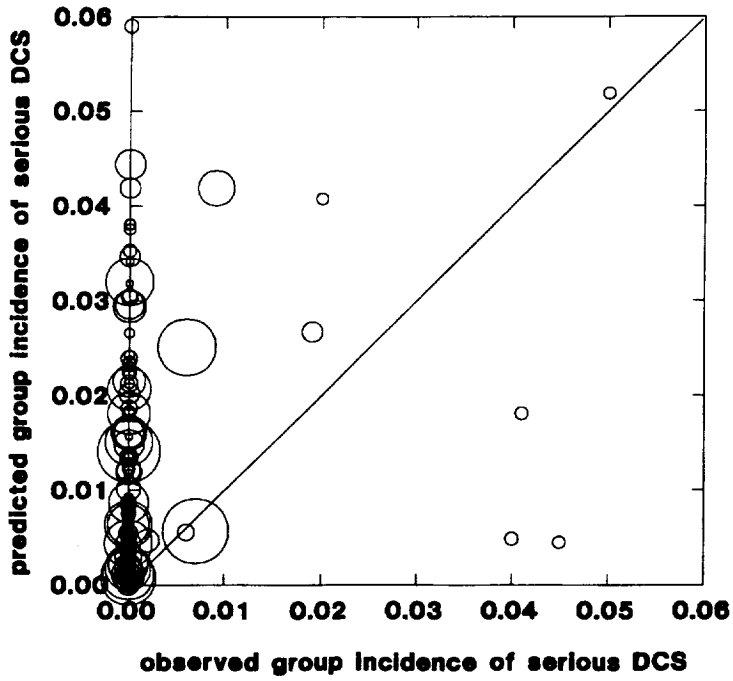

Fig. 11. The x- and y-axis are expanded to evaluate the goodness of fit in those tests where the observed incidence of serious DCS in 206 tests was ≤ 0.05. Three tests are not shown: n = 12 with an estimated incidence of 12.3%, but an observed incidence of zero percent; n = 14 with an estimated incidence of 6.1%, but an observed incidence of zero percent; and n = 21 with an estimated incidence of 11.7%, but an observed incidence of 4.8%.

Quantitative Assessment of Goodness of Fit

A computational method, as opposed to the previous visual method, is also available to assess goodness of fit. Equation 7 is the One-Sample χ^2 Test. The test compares an observed distribution to a theoretical one. The null hypothesis is that there is no difference between the distributions; any difference observed is simply due to chance. In the case where estimated always equals observed, the summed χ^2 is zero.

$$\chi^2 = \sum_{i=1}^{k} | O_i - E_i |^2 / E_i \qquad \text{Eq. 7}$$

where O_i = observed number in ith bin, E_i = expected number in ith bin, and k = number of bins. We accept the null hypothesis if the p-value is ≥ 0.05 for the computed χ^2, and n – 4 is the degrees of freedom, where n = 10 bins that the 258 tests were distributed into. The four in the calculation of the degrees of freedom is because there are four parameters estimated in the model. The data were combined into ten bins such that the estimated cases at very low values of r_c were about two. To reject the null hypothesis at $p < 0.05$ would require a computed χ^2 be < 12.59.

based on six degrees of freedom (from a χ^2 table). The summed χ^2 from Table VI was 118.5, with a resulting p-value <0.00001. Three bins, numbers 3, 6, and 8, show significant overestimation of serious DCS, while bins 4 and 9 show significant underestimation. Based on this analysis, we reject the null hypothesis, and conclude that the model does not account for all the variability observed in the outcome of serious DCS.

TABLE VI. RESULTS FROM ONE-SAMPLE χ^2 TEST

bin	tests	exposures	observed	estimated	χ^2
1	1 – 70	2,564	4	2.03	1.89
2	71 - 91	696	0	1.85	0.85
3	92 - 112	10,197	21	47.46	14.75
4	113 - 133	51,586	354	293.14	12.63
5	134 - 154	525	2	4.61	1.47
6	155 - 175	2,106	2	34.73	30.85
7	176 - 196	777	28	16.77	7.52
8	197 - 217	8,485	163	229.36	19.20
9	218 - 238	1,349	111	68.03	27.14
10	239 - 258	1,081	233	217	1.18
totals	258	79,366	918	915	118.51

Model Validation

A final method to assess goodness of fit is to evaluate, or validate, Eq. 5 with data not used to initially parameterize the model. Forty tests that provided 723 exposures are available that did not meet the initial selection criteria in that data on ascent rate was not available, and T_{alt} was not limited to 8 hr. The mean and standard deviation for variables in the 40 tests are: P2 = 5.05 ± 1.83 psia, T_{alt} = 4.3 ± 2.2 hr, TR based on 180 min $t_{1/2}$ = 1.33 ± 0.69, and exercise was present in 67% of the tests. Thirty-eight of the tests (637 exposures) had no case of serious DCS. The P(serious DCS) was computed for each test with Eq. 5, and the product of the probability and number of subjects in each test gives the estimated number of cases. The model estimated 2.5 cases in the 637 exposures where there were no observed cases. One test with 56 exposures had two cases of serious DCS, and the model estimated 14.8. The observed incidence in this test was 3.6% and the estimated was 26.4%. This test was particularly stressful in that an ascent to 3.0 psia was made with no prebreathe, and exercise was done over a 2-hr exposure. A second test with 30 exposures had a single case, and the model estimated 2.3 cases. This test was the same as above, except the exposure was 0.5 hr. Figure 12 shows the observed incidence compared to estimated incidence in the 40 tests. The model in a separate data set

overestimates the observations from stressful decompressions, but performed reasonably well with decompressions that provided some protection from DCS.

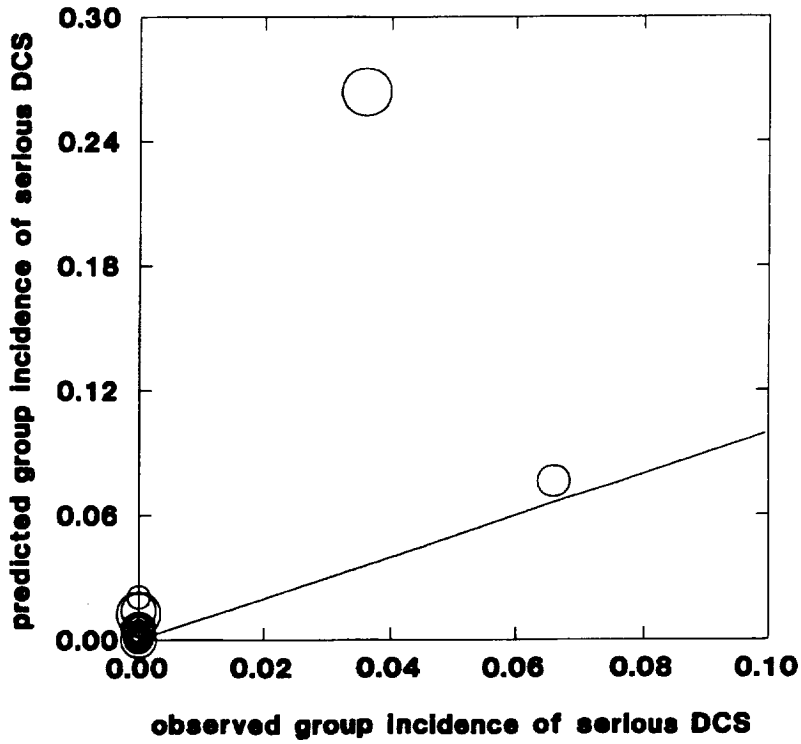

Fig. 12. Observed versus estimated incidence based on 40 validation tests not used to parameterize the probability model.

Discussion

Estimating any low probability event is a challenge. One advantage here is that cases of serious DCS were not likely missed compared to pain-only outcomes. A bias not to report a pain-only symptom is a constant concern in training, and even research settings. Subjects, often pilots and other aircrew in training, may have been reluctant, for fear of disqualification, to report mild symptoms during their training. Also, different investigators undoubtedly had different criteria for what qualified as a bonafide case of DCS, but a case of serious DCS would not likely be missed.

On the whole, Eq. 5 accounted for the observed group incidence, with 915 cases estimated and 918 observed in the complete data set. But there are notable cases where the model underestimated the risk. For example, there were three large circles below the identity line on Fig. 8 where the observed group incidence was between about 33% and 40%, but the estimated incidence was about 20%. The model often estimated very low incidence in tests with no cases of serious DCS, both in data used to fit the model and data used to validate the model. However, the model often overestimated the number of cases in those tests where serious DCS was

observed. We regard this as a limitation of the model since we cannot assume that the overestimation was due to a bias not to report a serious symptom. Clearly there is room for improvement, both in the model and the addition of other important explanatory variables, which are not available to us.

The addition of ascent rate as an explanatory variable did not improve the model, and yet this was expected to be important. Since tests with "explosive decompressions" were excluded from the HDSD, it may be that the range of remaining ascent rates was not great enough for this variable to make a significant contribution to the model, as it was in another model (18). Another limitation of the model is that it only applies to men. Using the model to estimate the risk for women may not be valid because this assumes that men and women respond equally to a stressful decompression, which has not been established. We also assume the contribution of any exercise toward the risk of serious DCS is constant regardless of the combinations of other variables in the model, and this is certainly not true. Finally, including information about the frequency of exercise and eight classifications of the type of exercise did not improve the model.

Limitations of this analysis are the lack of additional information about the individuals in the test, the absence of the failure time when the serious DCS symptom first appeared, the censoring of failure time in some tests that ended prematurely for other reasons, and our simple probability model. A model based only on four variables and fitted to retrospective data will not accurately estimate the risk of serious DCS for all possible hypobaric decompressions, including decompressions in astronauts adapted to microgravity. It is likely that our simple model based on results from men in altitude chambers would apply to similar men doing similar tasks in future altitude exposures, but we are less confident that it will apply to men and women during EVA. However, combining a few important variables into an abstraction of the true decompression dose that is then statistically optimized to a DCS response is a practical means to estimate the risk of serious DCS.

Our motivations to understand the variables associated with serious DCS were to quantify the risk from previous EVAs and then, if necessary, to develop new procedures to prevent it during future EVAs from the ISS. At no time in the past have EVAs had such a significant role in the success of a program as they will have with the ISS construction. The increased number of EVAs increases the likelihood of a serious case of DCS. Knowing how different explanatory variables reduce the risk of serious DCS can be exploited as prebreathe procedures are developed. Figure 3 showed an interval at $r_c \leq 0.00145$ where no serious DCS was ever reported. Future denitrogenation and decompression procedures for ISS should place EVA astronauts within this interval. However, the influence on the incidence of serious DCS from variables involved in adapting to and working within a space suit in microgravity are unknown. Changes in body fluid volumes, distributions, and resulting pressures within the circulatory system in space may influence the efficiency of denitrogenation, or the likelihood to form bubbles in the tissues and blood. For example, inactivity of the lower body before and during exposures in hypobaric chambers, called adynamia, has been shown to reduce the incidence of

DCS and venous gas emboli returning to the lungs (6,14). If this also applies to astronauts during EVA, then an important variable to reduce risk is missing from the model that would make the model more applicable to astronauts.

There is another practical aspect to knowing the risk of serious DCS for astronauts. The cost in terms of materials and training to provide for hyperbaric treatment capability on the ISS is not trivial. If there were no risk of DCS, then there would be no reason to provide an expensive treatment capability. This was the case during the Skylab program where 70% O_2 at a total pressure of 5.0 psia was breathed while in the space station. The engineering of the life support system assured that there was no risk of DCS since there was no N_2 supersaturation in the tissues during EVAs in the 3.75-psia space suit. Supersaturation defines a condition where the sum of all gas tensions (pressure) in a tissue exceeds the ambient pressure. Since DCS is not "engineered" out of the current U.S. and Russian space station programs, there is a finite risk of a serious case of DCS even when prebreathe procedures are accepted as safe. The difficult issue is to decide how much risk of serious DCS is acceptable to not require a hyperbaric treatment capability given that other less aggressive but still effective treatment options now exist. An option on the ISS and *Mir* does include returning the injured crewman to earth for a hyperbaric treatment, which would not be an option for a Mars mission.

In conclusion, Eq. 5 serves as a guide to quantify how manipulation of four variables before and after a depressurization can change the P(serious DCS) so that an acceptable level of risk is achieved. The estimate of risk applies to a group, not an individual, since there was no information about individuals in the model. Although we might be confident in a low estimate of risk in astronauts, it is not yet possible to identify which astronaut would be at greatest risk. Our worst-case estimate of serious DCS is 0.0019 (0.19%) for astronauts with the equivalent of a 4-hr prebreathe. This corresponds to a condition in which one case was reported in 2,498 exposures from 65 tests. Is this risk acceptable? Whereas it might be reasonable to accept the risk of a "pain-only" symptom (Type I DCS) under conditions where immediate treatment is available, it is unlikely that anyone would accept, or allow, a significant risk of serious DCS, regardless of the treatment capability. What defines a significant or acceptable risk of serious DCS is debatable. It depends on many factors such as the importance of success for a particular EVA, the availability of DCS treatment, and the programmatic impact to the National Aeronautics and Space Administration in the event of a serious case of DCS during an EVA.

References

1. Adler HF. Dysbarism. Aeromedical Review 1-64. San Antonio: Brooks AFB, 1964.

2. Beard S, Allen TH, et al. Comparison of helium and nitrogen in production of bends in simulated orbital flights. Aerospace Med 1967; 38:331-37.

3. Conkin J, Kumar KV, Powell MR, Foster PP, Waligora JM. A probabilistic model of hypobaric decompression sickness based on 66 chamber tests. Aviat Space Environ Med 1996; 67:176-83.

4. Conkin J, Bedahl SR, Van Liew HD. A computerized databank of decompression sickness incidence in altitude chambers. Aviat Space Environ. Med 1992; 63:819-24.

5. Conkin J, Foster PP, Powell MR. Evolved gas, pain, the power law, and probability of hypobaric decompression sickness. Aviat Space Environ Med 1998; 69:352-59.

6. Conkin J, Powell MR. Lower body adynamia as a factor to reduce the risk of hypobaric decompression sickness. Aviat Space Environ Med 2001; (in press)

7. Dixon JP. Death from altitude-induced decompression sickness: major pathophysiologic factors. In: The Proceedings of the 1990 Hypobaric Decompression Sickness Workshop. Pilmanis AA (ed.). Report AL-SR-1992-0005. San Antonio: Brooks AFB, 1992: p. 97 – 105.

8. Fryer DI. Subatmospheric Decompression Sickness in Man. Slough, England: Engelhard Hanovia International, Ltd. 1969.

9. Gray JS. Present status of the problem of decompression sickness. The Army Air Force School of Aviation Medicine Report 458. San Antonio: Randolph Field, 1944; pp. 1-46.

10. Hosmer DW Jr, Lemeshow S. Applied Logistic Regression. New York: John Wiley and Sons, 1989.

11. Ku HH. Notes on the propagation of error formulas. J Res National Bureau of Standards 1966; 70C:263-73.

12. Larrabee MG, Lilly JC, Comroe JH Jr., Hodes R. Decompression sickness during exposures to 38,000 feet, accompanied by exercise. Evaluation of a classification procedure. Committee on Aviation Medicine Report 137, National Research Council, 1943.

13. Motley HL, Chinn HI, Odell FA. Studies on bends. J Aviat Med 1945; 16:210-34.

14. Powell MR, Waligora JM, Norfleet WT, Kumar KV. Project ARGO - Gas phase formation in simulated microgravity. NASA Technical Memorandum 104762. Houston: Johnson Space Center; 1993.

15. Sedov AV, Mazin AN, et al. Probability of altitude decompression disorders when breathing oxygen containing human waste gases. Kosmicheskaya Biologiya I Aviakosmicheskaya Meditsina 1980; 14:36-39. USA Translation In: Space Biology and Aerospace Med 1980; 14:49-53.

16. Smedal HA, Brown EB, et al. Incidence of bends pain in a short exposure to simulated altitudes of 26,000, 28,000, and 30,000 feet. J Aviat Med 1946; 17:67-70.

17. Vakar MI, Mazin AN, et al. Relationship between onset of altitude-decompression disorders in man and barometric pressure level during intensive physical exercise. Kosmicheskaya Biologiya I Aviakosmicheskaya Meditsina 1977; 4:83-85. USA Translation In: Space Biology and Aerospace Med 1977; 4:112-15.

18. Van Liew HD, Burkard ME, Conkin J. Testing of hypotheses about altitude decompression sickness by statistical analyses. Undersea Hyperbaric Med 1996; 23:225-33.

19. Van Liew HD, Conkin J, Burkard ME. Probabilistic model of altitude decompression sickness based on mechanistic premises. J Appl Physiol 1994; 76:2726-34.

20. Weathersby PK, Homer LD, Flynn ET. On the likelihood of decompression sickness. J Appl Physiol 1984; 57:815-25.

21. Wilkinson L. SYSTAT: the system for statistics. Evanston: SYSTAT Inc., 1990. p. 342-87.

Appendix A: Sources of Data Used in Analysis of Serious DCS

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1. Adams JD, Dixon GA, Olson RM, et al. Preventing of bends during space shuttle EVAs using staged decompression. 1981 Preprints of the Aerospace Medical Association Scientific Meeting, 55-6, 1981. (AD144*)

2. Adams JD, Olson GM, Dixon GA. Use of the doppler precordial bubble detector in altitude decompressions. Preprints of the 1981 Annual Scientific Meeting of the Aerospace Medical Association, 260-61, San Antonio, Tx, 1981. (AD150)

3. Allen TH, Maio DA, Bancroft RW. Body fat, denitrogenation and decompression sickness in men exercising after abrupt exposure to altitude. Aerospace Med 1971; 42:518-24. (NW130)

4. Allen TH, Maio DA, Beard SE, Bancroft RW. Space-cabin and suit pressures for avoidance of decompression sickness and avoidance of decompression sickness and alleviation of fire hazard. J Appl Physiol 1969; 27:13-17. (AD611)

5. Anthony RA, Clarke RW, Liberman A, et al. Temperature and decompression sickness. CAM Report No. 136, 1943. (AD1430)

6. Anthony RA, Clarke RW, Liberman A, et al. Effects of local compression, impairment of venous return, and arterial tourniquet upon the intensity of established "bends" pain. CAM Report No. 143, 1943. (AD1431*)

7. Balldin UI, Borgstrom P. Intracardial bubbles during decompression to altitude in relation to decompression sickness in man. Aviat Space Environ Med 1976; 47:113-16. (AD237*)

8. Barer AS, Golovkin LG, et al. Probability of casson disease while wearing a space suit when exiting from a spacecraft with an atmosphere close to that of earth. Kosmicheskaya Biologiya I Aviakosmicheskaya Meditsina 1979; 13:37-42. USA Translation In: Space Biology and Aerospace Med 1979; 13:53-59. (AD817)

9. Barer AS, Vakar MI, et al. Probability of casson disease after pressure drop from 840 to 308 mmHg. Kosmicheskaya Biologiya I Aviakosmicheskaya Meditsina 1982; 16:26-28. USA Translation In: Space Biology and Aerospace Med 1982; 16:34-37. (AD818*)

10. Bateman JB. Susceptibility to decompression sickness: The effect of prolonged inhalation of certain nitrogen-oxygen mixtures compared with those of exposure to pure oxygen. CAM Report 364, NRC, 1944. (AD47)

11. Beard S, Allen TH, et al. Comparison of helium and nitrogen in production of bends in simulated orbital flights. Aerospace Med 1967; 38:331-37. (AD238)

12. Behnke AR. The value of preliminary oxygen inhalation for the prevention of decompression sickness during high altitude flight. National Research Council, Office of Scientific Research and Development. Report #114, 1942. (AD63*)

13. Bridge EV, Henry FM, et al. Nature and incidence of symptoms during and after artificial decompression to 38,000 feet for ninety minutes with exercise during exposure. J Aviat Med 1944; 15:1-12. (AD64)

14. Bridge EV, Henry FM, Williams OL, et al. Chokes: A respiratory manifestation of aeroembolism in high altitude flying. Ann Inter Med 1945; 22:398-407. (AD1318)

15. Cheetham RW. Incidence of decompression sickness in individuals tested in a decompression chamber situated at 4,700 feet. J Aviat Med 1947; 18:279-88. (AD1701)

16. Chernyakov IN, Glazkova VA, et al. Prevention of decompression disease applicable to conditions of multiple emergence into space. Kosmicheskaya Biologiya I Aviakosmicheskaya Meditsina 1976; 10:23-26. USA Translation In: Space Biology and Aerospace Med 1976; 10:33-38. (AD83)

17. Conkin J, Dierlam JJ. The impact of exercise and other factors on the incidence of venous gas emboli and decompression sickness in bends test 1,2, and 3. Houston: Johnson Space Center, Technology Inc., Contract NASA-16880, Project 0211-91, 1984. (AD91*)

18. Conkin J, Edwards BF, Waligora JM, Horrigan DJ Jr. Empirical models for use in designing decompression procedures for space operations. Houston: Johnson Space Center, NASA Technical Memorandum 100456, 1987. (1*)

19. Conkin J, Edwards BF, Waligora JM, Stanford J Jr, Gilbert JH III, Horrigan DJ Jr. Updating empirical models that predict the incidence of aviator decompression sickness and venous gas emboli for shuttle and space station extravehicular operations. Houston: Johnson Space Center, NASA Technical Memorandum 100456 Update, 1990. (ADNEW*)

20. Cooke JP. Interruption of denitrogenation by air-breathing. USAF School of Aerospace Medicine, Brooks AFB. Under NASA-MSC Contract T-82170, 1975. (NW119*)

21. Cooke JP, Bollinger RR, Richardson B. Prevention of decompression sickness during a simulated space docking mission. Aviat Space Environ Med 1975; 46:930-33. (AD616*)

22. Cooke JP, Robertson WG. Decompression sickness in simulated Apollo-Soyuz space missions. Aerospace Med 1974; 45:297-300. (AD118*)

23. Damato MJ, Highly FM, et al. Rapid decompression hazard after prolonged exposure to 50 percent oxygen-50 percent nitrogen atmosphere. Aerospace Med 1963; 34:1037-40. (AD612)

24. Degner EA, Ikels KG, Allen TH. Dissolved nitrogen and bends in oxygen-nitrogen mixtures during exercise at decreased pressure. Aerospace Med 1965; 36:418-25. (AD116*)

25. Dixon GA, Adams JD, Olson RM, Fitzpatrick EL. Validation of additional prebreathing times for air interruption in the Shuttle EVA prebreathing profile. 1980 Preprints of the Aerospace Medical Association Scientific Meeting, Anaheim, Ca., 16-17, 1980. (AD61*)

26. Dixon GA, Adams JD, Harvey WT. Decompression sickness and intravenous bubble formation using a 7.8 psia simulated pressure-suit environment. Aviat Space Environ Med 1986; 57:223-228. (AD126*)

27. Dixon GA, Krutz RW. Evaluation of 9.5 psia as a suit pressure for prolonged extravehicular activity. 23rd Annual SAFE Symposium Proceedings, 122-23, 1985. (AD431*)

28. Eatock BC, Gray GW, Ford GS. Evaluation with doppler ultrasonic bubble detection of standard Canadian forces aeromedical training altitude profiles. Canadian Forces School of Aeromedical Training. DCIEM Technical Communication No. 83-C-07, Downsview, Ontario, 1983. (AD159*)

29. Ferris EB, Webb JP, Engel G, Brown EW. A comparative study of decompression sickness under varied conditions of exercise, altitude, and denitrogenation. CAM Report No. 363, 1944. (AD1438*)

30. Ferris EB, Webb JP, Ryer HW, Engel GL, Romano J, Blakenhorn MA. The protective value of preflight oxygen inhalation at rest against decompression sickness. Washington D.C.: NRC Comm. on Aviation Med., Report No. 132, 1943. (AD73*)

31. Ferris EB, Webb JP, Ryer HW, Engel GL, Romano J, Blakenhorn MA. The influence of physical activity and physical relaxation on susceptibility to decompression sickness. Washington D.C.: NRC Comm. on Aviation Med., Report No. 126, 1943. (AD72*)

32. Gray JS. Present status of the problem of decompression sickness. The Army Air Force School of Aviation Medicine, Randolph Field, Texas. Report #458, pp. 1-46, 1944. (AD615)

33. Gray JS. Aeroembolism induced by exercise in cadets at 23,000 feet. Randolph AFB: Army Air Force, School of Aviation Med., Report No. 227, 1944. (AD76)

34. Gray JS, Mahady SCF. The prevention of aero-embolism in cadets at 45,000 feet by denitrogenation. CAM Report No. 315, 1944. (AD1436)

35. Gray JS, Mahady SCF, Masland RL. Studies on altitude decompression sickness III. The effects of denitrogenation. J Aviat Med 1946; 17:606-10. (AD1708)

36. Henry FM. Effects of exercise and altitude on the growth and decay of aviator's bends. J Aviat Med 1956; 27:250-59. (AD67)

37. Ivy AC, Atkinson AJ, Adler HF, et al. Incidence of symptoms of "bends and chokes" at 47,500 feet for one hour without exercise with intermittent pressure breathing. Washington D.C.: NRC Comm. on Aviation Med., Report No. 370, 1944. (AD1025)

38. Ivy AC, Atkinson AJ, Adler HF, et al. Pertaining to the effect of dextroamphetamine and preoxygenation plus dextroamphetamine on the incidence of bends and incapacitating bends and

chokes at 40,000 feet, for one hour. Washington D.C.: NRC Comm. on Aviation Med., Report No. 113, 1942. (AD1028)

39. Krutz RW, Dixon GA. The effects of exercise on bubble formation and bends susceptibility at 9,100 m (30,000 ft; 4.3 psia). Aviat Space and Environ Med 1987; 58(9,Suppl.):A97-9. (AD322*)

40. Krutz RW, Dixon GA, Harvey WT. Minimum pressure for a zero-prebreathe pressure suit. Fifteenth Intersociety Conference on Environmental Systems. SAE Report No. 851315, San Francisco, Ca., 1-3, 1985. (AD35*)

41. Kumar KV, Calkins DS, Waligora JM, Gilbert JH, Powell MR. Time to detection of circulating microbubbles as a risk factor for symptoms of altitude decompression sickness. Aviat Space Environ Med 1992; 63:961-64. (AD1506*)

42. Larrabee MG, Lilly JC, Comroe JH Jr., Hodes R. Decompression sickness during exposures to 38,000 feet, accompanied by exercise. Evaluation of a classification procedure. Washington D.C.: NRC Comm. on Aviation Med., Report No. 137, 1943. (AD1024)

43. Lawrence JH, Tobias CR, et al. A study of aero medical problems in a liberator bomber at high altitude. J Aviat Med 1945; 16:286-310. (AD1704)

44. Mackenzie CG, Riesen AH. The production of moderate exercise of a high incidence of bends. JAMA 1944; 124:499-501. (AD619)

45. Maio DA, Allen TH, Bancroft RW. Decompression sickness in simulated Apollo space-cabins. Aerospace Med 1969; 40:1114-18. (AD614)

46. Maio DA, Allen TH, Bancroft RW. Decompression sickness and measured levels of exercise on simulated Apollo missions. Aerospace Med 1970; 41:1162-65. (AD117)

47. Marbarger JP, Kadetz W, Variakojis D, Hansen J. The occurrence of decompression sickness following denitrogenation at ground level and altitude. J Aviat Med 1957; 28:127-133. (AD245*)

48. McIver RG, Beard SE, et al. Treatment of decompression sickness in simulated space flight. Aerospace Med 1967; 38:1034-36. (HB143*)

49. Motley HL, Chinn HI, Odell FA. Studies on bends. J Aviat Med 1945; 16:210-34. (AD911)

50. Norfleet WT. Protocol for flying after diving and NASA DCS Database. Houston: Johnson Space Center, 1992. (AD1622*)

51. Olson RM, Adams JD, Dixon GA. Effects of repeated altitude exposure on the incidence of decompression sickness. Aerospace Med., Assn., Preprints, Washington, D.C., 101-102, 1979. (AD69*)

52. Olson RM, Dixon GA, et al. An evaluation of the ultrasonic precordial bubble detector. Preprints of the 1981 Annual Scientific Meeting of the Aerospace Medical Association, 10-11. San Antonio, Tx, 1981. (AD149*)

53. Olson RM, Krutz RW, et al. An evaluation of precordial ultrasonic monitoring to avoid bends at altitude. Aviat Space Environ Med 1988; 59:635-39. (AD424*)

54. Powell MR, Waligora JM, Kumar KV. Hypobaric decompression in simulated null gravity; a model using chair-rest adynamia. Undersea Biomed Res 1995; 22 (Suppl):67. Also NASA DCS Database. Houston: Johnson Space Center, 1994. (AD1801*)

55. Powell MR, Waligora JM, Norfleet WT, Kumar KV. Project ARGO-gas phase formation in simulated microgravity. Houston: Johnson Space Center, NASA Technical Memorandum 104762, 1993. (AD1619*)

56. Robinson TW. High altitude endurance test. Randolph AFB: Army Air Force, Aeromedical Lab., Eng. Division, ENG-49-696-1E, 1943. (AD712*)

57. Robinson TW, Donnelly DP. High altitude tolerance tests. Randolph AFB: Army Air Force, Aeromedical Lab., Eng. Division, ENG-49-696-1G, 1944. (AD713*)

58. Ryder HW, Engel GL, et al. An assay of dextro-amphetamine for its protective value in decompression sickness. Washington D.C.: NRC Comm. on Aviation Med., Report No. 112, 1943. (AD1722*)

59. Sedov AV, Mazin AN, et al. Probability of altitude decompression disorders when breathing oxygen containing human waste gases. Kosmicheskaya Biologiya I Aviakosmicheskaya Meditsina 1980; 14:36-39. USA Translation in: Space Biology and Aerospace Med 1980; 14:49-53. (AD85)

60. Smedal HA, Brown EB, et al. Incidence of bends pain in a short exposure to simulated altitudes of 26,000, 28,000, and 30,000 feet. J Aviat Med 1946; 17:67-70. (AD243)

61. Smead KW, Krutz RW, Dixon GA, Webb JT. Decompression sickness and venous gas emboli at 8.3 psia. 24th Annual SAFE Symposium, 196-99, 1986. (AD430*)

62. Smith HW. The effect of anoxia on the incidence of decompression sickness at 35,000 feet. No. 2 Clinical Investigation Unit, RCAF, Regina, 1943. (HB134*)

63. Smith HW, Manning GW. The relationship between daily urinary output and the incidence of decompression sickness. Report to Director of Medical Service (Air). No. 2 Clinical Investigation Unit, RCAF, Regina, 1942. (HH25)

64. Vakar MI, Mazin AN, et al. Relationship between onset of altitude-decompression disorders in man and barametric pressure level during intensive physical exercise. Kosmicheskaya Biologiya I Aviakosmicheskaya Meditsina 1977; 4:83-85. USA Translation in: Space Biology and Aerospace Med 1977; 4:112-15. (AD816)

65. Vann RD, Gerth WA. Factors affecting tissue perfusion and efficacy of astronaut denitrogenation for extravehicular activity. F.G. Hall Hypo/Hyperbaric Center, Duke University Medical Center, Durham NC, March 31, 1995. (AD1807*)

66. Walder DN. Studies in the susceptibility to decompression sickness. University of Bristol, Bristol England. Thesis for Doctor of Medicine, 1947. (HH214*)

67. Waligora JM, Horrigan DJ Jr, Conkin J. The effect of extended O2 prebreathing on altitude decompression sickness and venous gas bubbles. Aviat Space Environ Med 1987; 58(9, Suppl):A110-12. (AD18*)

68. Webb JP, Engel GL, et al. The effect of pressure breathing on decompression sickness under different altitude conditions. University of Cincinnati College of Medicine Report No. 385, 1944. (AD79*)

69. Webb JT, Krutz RW, et al. An annotated bibliography of hypobaric decompression sickness research conducted at the crew technology division, USAF School of Aerospace Medicine, Brooks AFB, Texas from 1983-1988. USAFSAM-TP-88-10, Brooks AFB, Tx., 1988. (AD432)

70. Webb JT, Olson RM, et al. Oxygen toxicity during five simulated eight-hour EVA exposures to 100% oxygen at 9.5 psia. 18th Intersociety Conference on Environmental Systems. SAE Report 881071, 1988. (AD422*)

71. Webb JT, Pilmanis AA. Breathing 100% oxygen compared with 50% O2: 50% N2 reduces altitude-induced venous gas emboli. Aviat Space Environ Med 1993; 64:808-12. (AD1721)

72. Webb JP, Ryder HW, Engel GL, Romana J, Blankenhorn MB, Ferris EB. The effect of susceptibility to decompression sickness of preflight oxygen inhalation at rest as compared to oxygen inhalation during strenuous exercise. Washington D.C.: NRC Comm. on Aviation Med, Report No. 134, 1943. (AD249*)

73. Williams OL, Lyons WR, et al. The use of drugs for the prevention of decompression sickness. J Aviat Med 1946; 17:602-05. (AD1706*)

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The code in the parentheses identifies the location of the report in J. Conkin's filing system, and the * identifies that information exists on the individuals who participated in the test.

APPENDIX B: MAXIMUM LIKELIHOOD AND MODEL OPTIMIZATION

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Maximum likelihood is the preferred method to optimize unknown parameters in a model when the response variable is dichotomous. Maximum likelihood provides the probability that y = 1 given a value for "x", and is the method of choice when modeling a probability. The goal is to find a model that best describes the relationship between a response variable and a set of independent explanatory variables formulated into a model. The estimated P(serious DCS) is written as a function of the altitude exposure data, and the favored model:

$$P(\text{serious DCS}) = f(\text{altitude exposure data, model}), \qquad B1$$

where f is a risk function that the altitude exposure data and model are structured within.

The probability of no serious DCS is:

$$P(\text{no serious DCS}) = 1 - P(\text{serious DCS}). \qquad B2$$

If "y" is the actual outcome of serious DCS for a subject, where y = 0 for no serious DCS and y = 1 for serious DCS, then the estimated probability of the outcome is:

$$P(\text{outcome}) = P(\text{serious DCS})^{y} * (1 - P(\text{serious DCS}))^{(1 - y)}, \qquad B3$$

or in a more general form:

$$P(y_i) = (\pi(x_i))^{y_i} * (1 - \pi(x_i))^{(1 - y_i)} \quad y_i = 1,0 \qquad B4$$

where $\pi(x_i)$ is the conditional mean [P(serious DCS)] as modeled and for subject "i" with covariates x_i.

If the observed outcome is serious DCS (y = 1), then A3 gives P(serious DCS) from the probability model, Eq. 5 for example, and if the observed outcome is no serious DCS (y = 0), the equation gives P(no serious DCS), also from the probability model since [1 - P(serious DCS)] = P(no serious DCS). In the case where the probability model is always correct, P(outcome) equals one. In the case where the probability model is always wrong, the P(outcome) equals zero. The total estimated probability of all outcomes is given by the likelihood function:

$$L = \prod_{i=1}^{n} P(\text{outcome}), \text{ or } L = \prod_{i=1}^{n} (\pi(x_i))^{y_i} (1 - \pi(x_i))^{(1 - y_i)}, \qquad B5$$

where "n" is the number of subjects in the data set. A perfect model would produce a likelihood of one. The likelihood function expresses the probability of the observed data as a function of the unknown parameters. The maximum likelihood estimates of these parameters are chosen so as to maximize this function. Thus, the resulting estimates are those that agree most closely with the observed data.

The value of "L" is very small since it is the product of numbers between one and zero. It is convenient to take the natural logarithm of "L" to produce the log likelihood (LL) function:

$$LL = \sum_{i=1}^{n} \ln(P(\text{outcome})), \qquad \text{B6}$$

or

$$LL = \sum_{i=1}^{n} (y_i \ln(\pi(x_i)) + (1 - y_i) \ln(1 - \pi(x_i))), \qquad \text{B7}$$

and expanded with the definition of P(outcome):

$$LL = \sum_{i=1}^{n} [y_i \ln(P(\text{serious DCS})_i) + (1 - y_i) \ln(1 - P(\text{serious DCS})_i)]. \qquad \text{B8}$$

The value of LL is negative because it is the summation of the logarithms of positive numbers $\leq$ to one. The smallest negative number defines the best fit of the model to the observations. Note that even models with poor goodness of fits are still optimized to the data since the fitting routine provides a best fit to any model.

The SYSTAT Nonlin module estimates unknown parameters of nonlinear models. The module provides the option to construct a LOSS statement that is different from the standard least squares LOSS statement. In least squares, the idea is to minimize the sum of squared deviations of the observed values of "y" from the estimated values ($y^{\wedge}$) based upon the model, and data are used to estimate all unknown parameters in a model. Maximum likelihood estimation is accomplished in the Nonlin module by specifying the negative of the LL function as the LOSS statement. Parameter estimation in the Nonlin module is structured to minimize the positive LL, which is the same as maximizing the negative LL. The Quasi-Newton minimization technique is used to fit nonlinear models. The LOSS statement is:

$$\text{LOSS} = -(\text{SERIOUS} * \ln(\text{ESTIMATE}) + \text{NOSERIOUS} * \ln(1 - \text{ESTIMATE})), \qquad \text{B9}$$

where SERIOUS is the number of subjects in a group test with serious DCS, and NOSERIOUS is the remaining subjects in the test without serious DCS, and ESTIMATE is the evaluated P(Serious DCS). The computer evaluates the probability model (Eq. 5) for the first row of data in the data set with initial values for unknown parameters. The LL is then calculated from Eq. A9 for the same row of data using the ESTIMATE from the probability model. This procedure is repeated over all 258 rows in the data set and the LL is summed over all rows. A small adjustment is made in the values of the fitted parameters, based on the Quasi-Newton procedure, such that the summed LL is less than the previous summation. Iterations continue for parameters in the probability model to minimize the summed LL and until a predetermined convergence criterion is reached. In addition to parameter estimation using maximum likelihood, the module also computes asymptotic standard errors and the asymptotic correlation matrix by estimating the Hessian matrix after iterations have stopped, both of which are used in computing 95% confidence intervals for the estimates of P(serious DCS).

APPENDIX C: 258 GROUP DATA, LITERATURE REFERENCES, AND COMPUTED CUMULATIVE RISK FROM LOWEST TO HIGHEST

Number of male subjects	Number of serious DCS cases	Cumulative risk computed from Eq. 4	Literature reference for data
11	0	0.0000221	67
20	0	0.0000311	24
54	0	0.0000599	24
7	0	0.0000613	30
12	0	0.0000805	17
343	0	0.0001117	11
57	0	0.0001126	24
17	0	0.0001553	17
19	0	0.0001592	67
33	0	0.0002140	47
8	0	0.0002528	17
11	0	0.0002623	55
12	0	0.0003011	18
12	0	0.0003014	18
9	0	0.0003041	19
2	0	0.0003299	50
12	0	0.0003312	18
19	0	0.0003356	19
14	0	0.0003562	50
4	0	0.0003663	18
17	0	0.0004067	46
33	0	0.0004119	47
6	0	0.0004713	28
25	0	0.0004923	24
30	0	0.0005199	24
379	0	0.0005257	60
65	0	0.0005257	60
10	0	0.0006456	54
15	0	0.0006963	46
52	0	0.0007049	24
14	0	0.0007335	17
6	0	0.0007447	28
169	0	0.0007592	60
80	0	0.0007592	60
2	0	0.0007707	10
19	0	0.0007984	46
29	0	0.0008692	45
28	0	0.0008937	67
19	0	0.0009187	46

Number of male subjects	Number of serious DCS cases	Cumulative risk computed from Eq. 4	Literature reference for data
92	0	0.0011149	60
156	0	0.0011149	60
33	0	0.0011359	47
17	0	0.0011393	12
31	0	0.0011900	24
9	0	0.0012870	54
6	0	0.0012870	54
7	0	0.0012870	54
54	0	0.0013241	24
12	0	0.0013351	23
23	0	0.0014542	67
7	0	0.0014542	65
16	0	0.0014542	65
10	0	0.0014542	65
9	0	0.0014542	65
10	0	0.0014542	65
12	0	0.0014542	65
10	1*	0.0014542	65
12	0	0.0014841	23
11	0	0.0014888	21
31	0	0.0016031	3
12	0	0.0016620	23
8	0	0.0017443	40
29	0	0.0018096	45
137	0	0.0018110	3
70	0	0.0019010	46
14	1**	0.0020534	65
8	0	0.0020534	65
18	1***	0.0020534	65
15	1****	0.0020534	65
11	0	0.0020534	65
10	0	0.0020534	65
11	0	0.0021070	17
6	0	0.0021483	4
116	0	0.0021483	4
6	0	0.0021632	69
11	0	0.0021736	70
12	0	0.0021736	70
12	0	0.0021736	70
12	0	0.0021744	70
20	0	0.0021931	27
12	0	0.0022104	23
33	0	0.0022975	47
15	0	0.0023138	18
12	0	0.0023795	70

Number of male subjects	Number of serious DCS cases	Cumulative risk computed from Eq. 4	Literature reference for data
16	0	0.0026148	25
16	0	0.0027148	40
33	0	0.0029726	3
10	0	0.0029937	45
71	0	0.0030242	60
245	0	0.0030242	60
17	0	0.0031507	44
10	1	0.0031617	30
5	0	0.0032571	9
5	0	0.0033582	7
9	0	0.0034521	40
12	0	0.0035851	18
12	0	0.0035879	18
12	0	0.0036410	20
14	0	0.0037336	39
10	0	0.0038969	65
10	0	0.0038969	65
35	0	0.0040997	17
20	0	0.0041304	9
20	0	0.0042329	61
10	0	0.0042690	71
12	0	0.0043211	18
65	0	0.0043674	60
144	0	0.0043674	60
22	NASA 1+	0.0044859	17
19	0	0.0045711	25
13	0	0.0046881	20
9738	19	0.0046882	49
12	0	0.0046883	20
15	0	0.0046885	20
26	1	0.0048661	3
10	0	0.0049007	45
31	0	0.0051126	26
31	0	0.0051133	26
10	0	0.0051670	71
18	0	0.0051889	1
32	0	0.0052850	26
9	0	0.0053272	2
10	0	0.0054088	20
11	0	0.0054088	20
10	0	0.0054089	20
43	0	0.0054927	69
3	0	0.0055450	17
4337	26	0.0055902	49
46683	327	0.0057076	49

Number of male subjects	Number of serious DCS cases	Cumulative risk computed from Eq. 4	Literature reference for data
13	0	0.0061861	17
17	0	0.0062445	20
143	0	0.0064134	60
122	0	0.0064134	60
5	0	0.0065557	7
17	0	0.0066437	44
17	0	0.0067401	44
10	0	0.0068550	71
4	0	0.0070485	48
6	0	0.0072742	16
29	0	0.0075382	4
21	0	0.0075683	22
11	0	0.0080222	45
8	0	0.0081807	12
29	0	0.0081995	4
25	0	0.0085500	69
29	0	0.0085567	4
117	0	0.0087149	33
29	0	0.0087802	4
12	0	0.0090126	23
10	0	0.0092788	71
62	0	0.0101890	34
62	0	0.0101890	32
11	0	0.0117627	19
11	NASA 2++	0.0117627	19
68	0	0.0119851	8
15	0	0.0121555	55
59	NASA 0+++	0.0121555	41
14	NASA 1++++	0.0121555	55
22	0	0.0123891	22
42	0	0.0135366	52
14	0	0.0135366	2
23	0	0.0136429	51
23	0	0.0136429	51
195	0	0.0142129	33
82	0	0.0149730	53
143	0	0.0152264	8
4	0	0.0157824	12
83	0	0.0161814	15
100	0	0.0162003	32
585	0	0.0182575	59
434	0	0.0182575	64
24	1	0.0182826	62
126	0	0.0182826	63
15	0	0.0185912	8

Number of male subjects	Number of serious DCS cases	Cumulative risk computed from Eq. 4	Literature reference for data
35	0	0.0188430	3
23	3	0.0200716	56
23	3	0.0200716	56
50	0	0.0204305	38
35	2	0.0207115	66
55	8	0.0207115	66
128	0	0.0209092	32
38	0	0.0214761	69
14	0	0.0214761	39
90	0	0.0217385	35
90	0	0.0217385	35
17	0	0.0225183	44
27	0	0.0227023	72
27	5	0.0227023	30
13	0	0.0232692	29
8	0	0.0234289	9
20	0	0.0237584	9
21	0	0.0237584	9
24	2	0.0240438	57
24	5	0.0240438	57
36	0	0.0241504	23
14	0	0.0245397	29
180	1	0.0254102	32
14	0	0.0269339	44
7664	145	0.0270627	49
27	5	0.0283400	31
27	5	0.0283400	31
14	2	0.0290479	29
93	0	0.0298568	32
78	0	0.0300170	8
35	0	0.0308453	3
14	3	0.0309177	48
29	0	0.0310131	4
14	1	0.0321544	44
5	0	0.0323172	7
145	0	0.0325107	32
6	0	0.0347234	4
49	0	0.0352455	64
25	0	0.0358841	12
18	0	0.0382146	44
15	1	0.0387692	44
18	0	0.0387692	44
15	0	0.0387731	36
204	4	0.0415954	32
50	0	0.0427898	38

Number of male subjects	Number of serious DCS cases	Cumulative risk computed from Eq. 4	Literature reference for data
105	1	0.0427898	38
84	0	0.0454109	59
77	6	0.0455288	35
121	12	0.0459043	5
112	18	0.0459043	5
223	11	0.0532187	32
23	7	0.0537845	56
23	3	0.0537845	56
33	3	0.0587407	12
27	3	0.0608337	72
27	0	0.0608337	72
27	3	0.0608337	30
14	1	0.0623528	29
14	1	0.0623528	29
29	2	0.0624716	68
14	0	0.0625533	29
24	8	0.0644286	57
24	8	0.0644286	57
94	20	0.0853625	14
29	11	0.1022634	68
29	10	0.1213644	68
21	1	0.1244325	73
12	0	0.1315500	23
24	5	0.1630117	58
24	6	0.1630117	58
27	2	0.1630117	31
14	4	0.1670823	29
14	1	0.1670823	29
14	1	0.1670823	29
14	2	0.1670823	29
50	3	0.1790864	37
29	13	0.2158145	68
167	60	0.2230230	13
90	36	0.2257103	14
136	44	0.2257103	14
118	12	0.2260429	43
36	2	0.2640416	6
204	12	0.2748659	42
29	8	0.5882192	68

* from Duke University (1995), numbness in right hand that appeared 1 hr into test, and cleared on descent from 4.3 psia to site pressure. No hyperbaric treatment provided.

** from Duke University (1995), dizziness, nausea, and hot flash in head. No hyperbaric treatment provided.

*** from Duke University (1995), blurred vision during test. Treatment Table 6 provided.

**** from Duke University (1995), numbness and tingling in left shoulder. Treatment Table 6 provided.

+ from NASA/JSC (1982), sudden onset of fatigue, cold sweat, and skin mottling on chest after report of pain in right knee. No hyperbaric treatment provided, but 2 hr of ground level oxygen.

++ from NASA/JSC (1989), first case reported pain in right knee, headache, and later blurred vision. No hyperbaric treatment provided, but 2 hr of ground level oxygen. Second case reported pain in hands, pain in right knee, then later pain behind right eye with throbbing headache. Treatment Table 6 provided.

+++ from NASA/JSC (1990), classified as Type II based only on skin mottling on right side of chest 2 hr into exposure, but not counted as serious DCS in this analysis. Treatment Table 5 provided.

++++ from NASA/JSC (1992), had skin mottling on chest during test plus hypotension on standing after test, which may have been due to an extensive bed rest period. Treatment Table 5 provided.

NOTES

$S(t) = e^{-H(t)} = e\,[-\int_0^t h(x)\,dx]$, where $H(t) = r_c$ and $h(x) = r_i$.

r_i does not have to be a function of time, but the integration of r_i with respect to time will accumulate risk.

$F(t) = 1 - S(t)$

P(serious DCS) = $1 - e^{-r_c}$,

let P(serious DCS) = y and r_c = x, and solve for r_c

$y + e^{-x} = 1$
$e^{-x} = 1 - y$
$-x = \ln(1 - y)$
$x = -\ln(1 - y)$

==========

$r_c = -\ln[1 - P(\text{serious DCS})]$ = Eq. 2 =

$0.000613 * TR^{4.267} * (1 + (exer * 4.752)) * [(1 / 1.794^2) * (1 - (1.794 * T_{alt} + 1) * e^{-1.794 * T_{alt}})]$

$r_i = d(-\ln[1 - P(\text{serious DCS})]) / dt$ = Eq. 4 =

$0.000613 * TR^{4.267} * (1 + (exer * 4.752)) * (t * e^{-1.794 * t})]$

four hr prebreathe (4.6 / 4.3 = 1.069), with exercise at 4.3 psia, and after six hr at 4.3 psia.

r_i = ******** is the rate $d(-\ln[1 - P(\text{serious DCS})]) / dt$ at the second hr. The integration with respect to T_{alt} over the two hr gives:

$r_c = -\ln[1 - P(\text{serious DCS})] = 0.00146$

Rpt# 382 is the one without exerfreq included (n = 21)

Threshold of Serious DCS at Low r_c

at $r_c \leq 0.0045$ there are 109 tests with total exposures = 3,687. There are six tests with serious DCS:

exposures	serious	serfrac	r_c	institution
4-hr PB, 6-hr no exercise at 4.3 psia			0.000254	computed from model
10	1	10%	0.00145	Duke, 1995
4-hr PB, 6-hr exercise at 4.3 psia			0.00146	computed from model
14	1	7.1%	0.00205	Duke, 1995
18	1	5.5%	0.00205	Duke, 1995
15	1	6.7%	0.00205	Duke, 1995
10	1	10%	0.00316	NRC Comm. on Aviat. Med., 1943
22	1	4%	0.00449	NASA staged 10.2 psia
9,738	19	0.2%	0.00469	report by Motley, 1945
26	1	3.8%	0.00487	report by Allen, 1971
4,337	26	0.6%	0.00559	report by Motley, 1945
46,683	327	0.7%	0.00571	report by Motley, 1945

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13. ABSTRACT *(Maximum 200 words)*
It is important to understand the risk of serious hypobaric decompression sickness (DCS) to develop procedures and treatment responses to mitigate the risk. Since it is not ethical to conduct prospective tests about serious DCS with humans, the necessary information was gathered from 73 published reports. We hypothesize that a 4-hr 100% oxygen (O2) prebreathe results in a very low risk of serious DCS, and test this through analysis. We evaluated 258 tests containing information from 79,366 exposures in altitude chambers. Serious DCS was documented in 918 men during the tests. A risk function analysis with maximum likelihood optimization was performed to identify significant explanatory variables, and to create a predictive model for the probability of serious DCS. Useful variables were Tissue Ratio, the planned time spent at altitude, and whether or not repetitive exercise was performed at altitude. A prebreathe and decompression profile Shuttle astronauts use for extravehicular activity (EVA) includes a 4-hr prebreathe with 100% O2, an ascent to P2 = 4.3 lb per sq. in. absolute, and a Talt = 6 hr. Given 100 Shuttle EVAs to date and no report of serious DCS, the true risk is less than 0.03 with 95% confidence. It is problematic to estimate the risk of serious DCS since it appears infrequently, even if the estimate is based on thousands of altitude chamber exposures. The true risk to astronauts may lie between the extremes of the confidence intervals since the contribution of other factors, particularly exercise, to the risk of serious DCS during EVA is unknown. A simple model that only accounts for four important variables in retrospective data is still helpful to increase our understanding about the risk of serious DCS.

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