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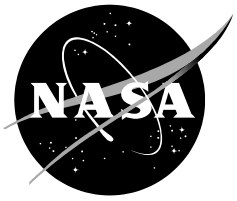

Probability of Decompression Sickness and Venous Gas Emboli from 49 NASA Hypobaric Chamber Tests with Reference to Exploration Atmosphere

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April 2020

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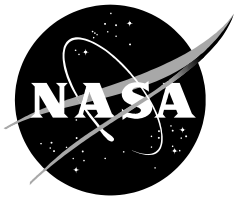

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EXECUTIVE SUMMARY

Introduction: Decompression sickness (DCS) is a complex biophysical event; it combines human perception of pain, for instance, and the presence of a gas phase in the tissues. Living tissues are complex and dynamic. Micronuclei and later bubbles may or may not form given what appears to be the same conditions. Even when bubbles grow, symptoms may or may not develop under what appears to be the same conditions. Therefore, at this time it is appropriate to consider DCS as a probabilistic rather than a deterministic event. **Methods:** Probabilistic models about hypobaric DCS and venous gas emboli (VGE) require a large amount of quality research data, a definition of decompression dose using physical and physiologic variables, and a flexible analytical approach that can quantify the association between each outcome and all covariates of interest (assuming independence between DCS and VGE) and then ultimately be extended to acknowledge dependencies between DCS and VGE. Our DCS and VGE data are from 1,031 hypobaric decompressions from 1983 to 2016. A total of 577 humans participated in 49 hypobaric chamber tests to evaluate denitrogenation procedures used by astronauts in the Space Shuttle and International Space Station programs. We defined decompression dose as the ratio of computed nitrogen tension in a theoretical 360-minute half-time compartment to ambient pressure, which accounts for denitrogenation and exposure pressure as well as explanatory variables such as age, sex, body mass index, and the presence or absence of ambulation as part of exercise at the exposure pressure. A parametric survival model, using a log-logistic distribution, was used to quantify the time to development of DCS, VGE, and Grade IV VGE. **Results:** Our survival estimates are applicable to simple hypobaric decompressions, such as depressurizations in 5 to 30 minutes to exposure pressures between 4 and 10 pounds per square inch absolute (psia) and after minutes to hours of denitrogenation, either under resting or exercise conditions to accelerated denitrogenation. The regressions are applicable to exposures between 2 to 6 hours and under conditions of ambulation or no ambulation as part of exercise at the test pressure. We estimate that an exposure to 4.3 psia with simulated extravehicular activity (EVA) that includes ambulation after equilibration to the exploration atmosphere at 8.2 psia with a 34% oxygen atmosphere will result in 3.1% DCS (1.8% to 5.2 95% confidence interval), 23.2% VGE (16.7 to 31.2%), and 8.5% Grade IV VGE (4.7 to 14.7%) in equal samples of men and women exposed for 6 hours. **Discussion:** Probabilistic models for DCS, VGE, and Grade IV VGE can be used to inform those that plan future EVAs. Their applications are useful to quantify the risk of DCS and VGE in astronauts that perform EVAs in low-pressure space suits while in space or while exploring the surfaces of the moon or Mars.

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ACRONYMS

AIC	Akaike Information Criterion
ATA	Atmospheres Absolute
BGI	Bubble Growth Index
BIC	Bayesian Information Criterion
BMI	Body Mass Index
CI	Confidence Interval
DCS	Decompression Sickness
DT	Doppler Technician
EA	Exploration Atmosphere
EVA	Extravehicular Activity
GIV	Grade IV venous gas emboli
JSC	Johnson Space Center
kg	kilogram
mHz	megahertz
mL	milliliter
mmHg	millimeter of mercury
N_2	nitrogen
O_2	oxygen
P2	ambient pressure
P_I0_2	inspired partial pressure of oxygen
PN_2	partial pressure of nitrogen
PO_2	partial pressure of oxygen
psia	pounds per square inch absolute
SD	Standard Deviation
SE	Standard Error
TBDM	Tissue Bubble Dynamics Model
TR	Tissue Ratio
VGE	Venous Gas Emboli
xEMU	Exploration Extravehicular Mobility Unit

1.0 INTRODUCTION

Minimizing the risk of hypobaric decompression sickness (DCS) in aviators and astronauts is possible once this occupational hazard is understood (Conkin 1994). DCS in all its myriad forms and manifestations is fundamentally linked to evolved gas in the body (Conkin 2001). A fundamental axiom about DCS is that a transient gas supersaturation exists where the sum of all gas partial pressures in that region is greater than the ambient pressure opposing the release of the gas. The metastable condition may resolve with a phase transition in the presence of micronuclei. Compliant tissues may accommodate some of the excess mass (moles) of gas in the form of bubbles and cause no symptoms or opposed by elastic tissues resulting in a deformation pressure that is perceived. The probability of DCS increases as the evolved gas dose increases; this is a necessary but not sufficient condition in the mechanical view of DCS. Not all of the complex biophysical processes responsible for evolved gas in the tissue are known. Even less is known about the linkage between evolved gas and subsequent signs or symptoms of DCS (Conkin *et al.* 1998a). Therefore, a probabilistic approach is pursued to quantify the time to DCS.

DCS signs and symptoms are the overt manifestations of evolved gas in the body. DCS is the "actionable" outcome; it may limit the success of an extravehicular activity (EVA) and would certainly initiate a treatment protocol. The presence of venous gas emboli (VGE) is a covert manifestation of the decompression stress; they are not felt by the astronaut and are detectable only with the aid of ultrasound technology. The exact origin of VGE is unknown. Nitrogen (N_2) molecules in excess of what can remain in solution at the prevailing pressure appear in the venous circulation. They cling to the vascular endothelium to then dislodge into the circulation through muscle contractions of a limb. We used ultrasound technology to detect bubbles in the venous blood flowing to the lungs as an unbiased assessment of decompression stress.

Therefore, a probabilistic approach is pursued to quantify the time to DCS and time to VGE. Survival models were constructed separately for each outcome (assuming DCS and VGE are independent). For outcome Y and time T, we aim to estimate $P(Y\ T < t)$ as a function of hypobaric exposure and demographics and other biophysical measurements. For notational convenience, we drop $T < t$ in the probability statement, but note it in the text [i.e., $P(Y\ T < t) = P(Y\ )$].

1.1 Decompression Sickness Grading via Medical Officer

DCS signs and symptoms are numerous since a growing bubble(s) can mechanically distort any tissue and hinder the supply of arterial blood or removal of venous blood from any tissue. An educated subject reports a symptom of DCS and a sign is documented by trained observers conducting the test. A Medical Officer with specialized training makes a diagnosis of DCS as pain-only Type I, Type II neurological manifestations, or cutaneous involvement. Any sign or symptom diagnosed as DCS is our dichotomous outcome variable along with the elapsed time from the start of the altitude exposure to the first sign or symptom.

1.2 Venous Gas Emboli Grading via Doppler Ultrasound

About every 12 to 16 minutes during the hypobaric exposure, the subject would suspend their simulated EVA and submit to a 4-minute period of precordial bubble monitoring. Denitrogenation (prebreathe) protocols minimize the risk of DCS and VGE during EVA. It is necessary to approximate the type and intensity of physical work as part of our EVA simulations since this influences the risk of DCS and VGE during an actual EVA. About 75% of the time at altitude, subjects were physically active at various exercise stations (Conkin *et al*. 2014).

The bubble monitoring by a Doppler Technician (DT) was often done with the subject in a supine position but sometimes was performed in a seated position depending on the specific study. The monitoring was done with a 5-mHz ultrasound probe early in the testing from 1983 to 2000 and then with a 2.5-mHz probe past 2000. Once a quality blood flow signal through the pulmonary artery was established, the subject would flex each limb 3 times in sequence to encourage VGE that are present to dislodge from the vascular endothelium of the limb. This technique improved the grading scheme because a bolus of bubbles carried by the venous return to the right ventricle became available for grading. A person outside the chamber would grade the intensity of bubble sounds from each of the 4 limbs on the 0–IV Spencer Scale (Spencer 1976).

Grade 0:	The complete lack of bubble signals in all cardiac cycles.
Grade I:	The occasional bubble signal detected in a cardiac cycle with the majority of cardiac cycles free of bubble signals.
Grade II:	When many, but less than half, of the cardiac cycles contain bubble signals.
Grade III:	When most of the cardiac cycles contain bubble signals, but not overriding the cardiac motion signals.
Grade IV:	When bubble signals are detected continuously through the cardiac cycles such that the signal overrides the amplitude of the cardiac motion and blood flow signals.

One consistent observation about subjects at the Johnson Space Center (JSC) is that Type I pain-only DCS after significant denitrogenation occurred predominantly in the lower body, particularly with that part of the body associated in or around the patella of the knee. Subjects often noticed a fullness, awareness, or a frank pain when the leg was horizontally flexed with the body in a supine position. While standing or walking, the pain, fullness, or awareness would sometimes abate only to return when the leg was once again horizontally flexed during the bubble-monitoring interval.

A successful EVA is when there were no symptoms that compromised the goals of the exposure or compromised the health of the astronaut. It is common for a symptom-free decompression to be associated with detectable VGE (Conkin *et al*. 1998b). A healthy lung is able to tolerate a small embolic load, but if possible the magnitude and frequency of pulmonary embolic insult should be minimized. To that end, survival models for VGE and Grade IV VGE onset are provided to assess the P(VGE $T < t$) and P(Grade IV VGE $T < t$) associated with the hypobaric exposure. A word about survival notation: Survival models are used to characterize the probability of an event up to a specific time T where t is the

planned exposure time of a test. When an estimate of P(DCS) or P(VGE) is provided, the specific time *T* is always mentioned. Grade IV VGE is a categorical designation for the highest intensity of bubble sounds in the pulmonary artery detected by ear using a Doppler ultrasound bubble detector in the precordial position.

2.0 METHODS

2.1 Log-logistic Accelerated Survival Models for Decompression Sickness, Venous Gas Emboli, and Grade IV Venous Gas Emboli

The general techniques of survival analysis are described elsewhere (Cox & Oakes 1984, Lee 1992). We have applied log-logistic survival models in other applications when estimating the probability of time to DCS or venous gas emboli up to time *t* [P(DCS $T < t$), P(VGE $T < t$)] since the hazard function is non-monotonic; the instantaneous failure rate increases to a maximum and then decreases during the hypobaric exposure (Conkin *et al.* 1996a,b, 1998). This is the pattern for the rate of DCS and VGE observed through time. All analyses were done using the Survival Module in SYSTAT® version 13 software (Steinberg *et al*. 2009).

We now list, define, and briefly summarize the explanatory variables (covariates) and the outcome (binary response) variables.

2.2 Explanatory Regression Variables

- Sex (SEX): 1 = male (n = 834 male-exposures), 0 = female (n = 197 female-exposures), 80.9% male
- Age (AGE): 32.1 years ± 7.9 standard deviation (SD), with 32.5 ± 8.1 for female and 32.0 ± 7.8 for male
- Body Mass Index (BMI): height (m)/weight $(kg)^2$, 24.2 ± 2.8, with 24.7 ± 2.5 for male and 22.1 ± 2.6 for female
- Tissue Ratio (TR): computed $P_{tis}N_2$ (psia)/P2 (psia), where $P_{tis}N_2$ is the computed nitrogen tension in a theoretical 360-minute half-time tissue compartment, P2 is ambient pressure in the hypobaric chamber, 1.598 ± 0.318. P2 is the lowest ambient pressure in the hypobaric chamber at the beginning of a test, between 10.1 and 4.3 psia. TR is a quantification of decompression dose.
- Ambulation (AMB): 1 = ambulation as part of exercise at P2, 0 = no ambulation as part of exercise at P2, 59.3% ambulation
- Repressurization (REP): a portion of the prebreathe included a 30-minute depressurization to 10.2 psia and a 30-minute exposure to 10.2 followed by a 5-minute repressurization to 14.7 psia to complete the balance of prebreathe before a final 30-minute depressurization to 4.3 psia, 27.6% of all exposures with this condition

- Exposure Time (t): 126 extended exposure times at 10.2 psia with 15 ± 5 hours duration, 905 exposures to mean P2 of 4.85 ± 1.15 psia for 4 ± 1 hour, with grand mean for all 1,031 exposure times as 5.35 ± 4.09 hours

2.3 Outcome Regression Variables

- DCS: 1 = signs or symptoms diagnosed as DCS by an independent Medical Officer, either classified as Type I or II DCS usually during exposure to P2 but in a few cases DCS first reported after the test, 0 = no DCS signs or symptoms reported. In survival analysis the time to report DCS is described when DCS = 1, and the censored time is the duration of the exposure at P2 when DCS = 0.
- VGE: 1 = any detected Grade of VGE within the pulmonary artery during interval monitoring at P2, 0 = no VGE detected during the exposure to P2. The interval between VGE monitoring was about 15 minutes for each subject. Interval censoring was used in the analysis of VGE survival. The time to detect VGE is described when VGE = 1, accounting for the interval of uncertainty between VGE = 0 and then VGE = 1, and the censored time is the duration of the exposure at P2 when VGE = 0.
- Grade IV VGE (G IV VGE): 1 = detection of Grade IV VGE any time during interval monitoring at P2, 0 = no Grade IV VGE detected during exposure to P2. Interval censoring was also used in the analysis of Grade IV VGE and accounted for the interval of uncertainty between when VGE grade was ≤ III and then VGE grade = IV.

2.4 Denitrogenation

One must account for denitrogenation before the hypobaric exposure as part of the decompression dose. We use the same 360-minute half-time compartment for tissue N_2 uptake and elimination for all prebreathe conditions that do not include exercise during prebreathe. Aviators and astronauts are initially in an environment where they are in equilibrium with atmospheric N_2 partial pressure (PN_2), so any prebreathe procedure first eliminates N_2 from well-perfused tissues. Denitrogenation protocols used or tested by NASA are conservative; meaning that significant denitrogenation has occurred prior to depressurization. Our conservative methods leave only tissues that retain N_2 as possible sources of DCS symptoms, discounting embolic insult. Therefore, in our modeling of DCS and VGE risk, computed $P_{tis}N_2$ is an essential component of decompression dose, as defined by the ratio of computed $P_{tis}N_2$ to P2 at the start of the hypobaric exposure.

Initial equilibrium tissue N_2 tension $P_{tis}N_2(0)$ is taken as ambient PN_2, 11.61 psia at 1 ATA. The 1% contribution of argon in normal air is treated as if it were N_2. A prebreathe protocol often takes place over a long interval of time during which a resting subject breathes 100% oxygen (O_2) by mask or in the EVA suit. However, these protocols can also be complex, for example when the total prebreathe time T is divided into m smaller intervals $(0, t_1)$, (t_1, t_2), . . .,$(t_{m-1}, T=t_m)$, with varying amounts of exercise performed during some of the intervals to accelerate denitrogenation.

Equation 1 describes the change in $P_{tis}N_2$ when there is a change in ambient PN_2 from $P_{a,i-1}$ to a new level $P_{a,i}$ over the i-th time interval $\Delta t_i = (t_{i-1}, t_i)$.

$$P_{tis}N_2(i) = P_{a,i-1} + \left(P_{ai} - P_{a,i-1}\right)\left(1 - e^{-k_i \Delta t_i}\right) + s_i \Delta t_i - \frac{s_i}{k_i}\left(1 - e^{-k_i \Delta t_i}\right), \quad \text{Eq. 1}$$

where $P_{tis}N_2(i)$ is the new value of $P_{tis}N_2$ and the average rate of change (s_i) of PN_2 in the breathing gas mixture is $((P_{ai} - P_{a,\,i-1}) / \Delta t_i.)$. The rate constant k_i varies with exercise and is expressed as a function of normalized O_2 consumption rate $\dot{V}_{O_2 i}$ expressed as mL $O_{2(STPD)} \times kg^{-1} \times min^{-1}$:

$$k_i = \frac{e^{\lambda \dot{V} O_2 i}}{519.37}, \quad \text{Eq. 2}$$

where λ is assumed equal to 0.03 on the basis of a previous analysis of exercise prebreathe (Conkin *et al*. 2004). In prebreathes that contain intervals of rest and exercise, the resting O_2 consumption rate is assumed as 3.5 mL $O_2 \times kg^{-1} \times min^{-1}$, and thus k_i is 0.00214; when the O_2 consumption rate during a brief bout of exercise is 35 mL $O_2 \times kg^{-1} \times min^{-1}$, then k_i is 0.00550. In prebreathe protocols that contain no exercise, the total prebreathe time T consists of only one interval ($m = 1$) and O_2 consumption rate is negligible. In this case, Eq. 2 is evaluated with $\dot{V}_{O_2} = 0$ and yields $k = 1/519.37 = 0.00192$. This value corresponds to a 360-minute half-time through the relation $t_{1/2} = ln(2)/k$. Changes in PN_2 occur through a change in ambient pressure while breathing either any constant $O_2 - N_2$ mixture or an $O_2 - N_2$ mixture that changes in time while at a constant pressure. In most applications, 100% O_2 is breathed by mask during the prebreathe and depressurization, during the low-pressure EVA simulation, and during repressurization. In this case, ambient PN_2 abruptly decreases to zero ($P_{ai} = s_i = 0$, for $i > 0$) in all phases of the prebreathe, so Eq. 1 reduces to Eq. 3:

$$P_{tis}N_2(i) = P_{a,i-1} - P_{a,i-1}\left(1 - e^{-k_i \Delta t_i}\right). \quad \text{Eq. 3}$$

Figure 1 shows the relationship between O_2 consumption rate normalized by body weight to a theoretical half-time tissue compartment to quantify denitrogenation and renitrogenation during a prebreathe.

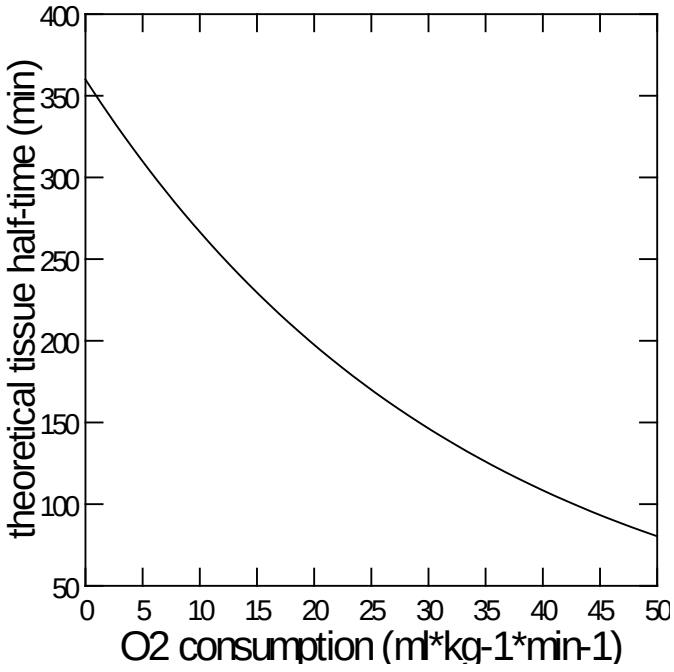

Fig. 1. The association between O_2 consumption rate and theoretical tissue half-time. As body weight normalized O_2 consumption rate increases the theoretical half-time decreases in accordance with $t_{1/2i} = ln(2) / \frac{e^{\lambda \dot{V}O_2 i}}{519.37}$, where $\lambda = 0.03$.

2.5 Rules to Apply Equation 1

There are 4 rules to apply Eq. 1:

1) If normalized O_2 consumption rate is known for exercise, transition from exercise to rest, and rest intervals during all intervals of the prebreathe, then apply those O_2 consumption rates to Eq. 1, where *k* is defined in Eq. 2, to compute final $P_{tis}N_2$ for the prebreathe. We assigned a normalized steady-state O_2 consumption rate for intervals of exercise based on an exercise prescription for each subject from a prior VO_{2pk} measurement. Our prebreathe protocols consisted of exercise and rest intervals. In those cases where exercise preceded rest, we reasoned that the transition from exercise to rest would not be instantaneous. We estimated an O_2 consumption rate for the transition between exercise and rest based on total O_2 consumption of the prebreathe protocol from a representative sample of subjects. The assigned O_2 consumption rate during the transitional intervals was such that the total O_2 consumption for the entire prebreathe was similar to that in our representative sample of subjects (see Conkin *et al*. 2004 for details).

2) If the prebreathe has no exercise, then use 0 mL $O_2 \times kg^{-1} \times min^{-1}$ in Eq. 1, where *k* is defined in Eq. 2.

3) If the prebreathe includes exercise, then use 3.5 mL $O_2 \times kg^{-1} \times min^{-1}$ in Eq. 1, where *k* is defined in Eq. 2, in intervals of rest after accounting for O_2 consumption rate during the transition from exercise to rest. If transitional O_2 consumption rate is not available, then the user can assume an

instantaneous transition from exercise to rest. However, this approach results in a greater probability of DCS, VGE, and Grade IV VGE because the final TR for the regression models will be larger than if a transitional O_2 consumption rate is provided. Our rule is to compute the difference between the steady-state O_2 consumption rate during exercise and 3.5 mL $O_2 \times kg^{-1} \times min^{-1}$ for rest and then take half the difference and assign that value to the first 5 minutes of the rest interval. For example, a 15-minute interval of exercise prebreathe at 31.5 mL $O_2 \times kg^{-1} \times min^{-1}$ is followed by a 60-minute interval of resting prebreathe. The transitional O_2 consumption rate is $(31.5 - 3.5)/2 = 14$ mL $O_2 \times kg^{-1} \times min^{-1}$ for the first 5 minutes of the 60 minute rest interval and 3.5 mL $O_2 \times kg^{-1} \times min^{-1}$ for the remaining 55 minutes.

4) The onset of exercise from resting is considered instantaneous with the entire exercise interval assigned the steady-state O_2 consumption rate.

3.0 RESULTS

Figure 2 shows the cumulative proportion of failure times for VGE and Grade IV VGE detected in the pulmonary artery and reported DCS symptoms from 49 hypobaric chamber tests conducted from 1983 to 2016 taken from the NASA Hypobaric Decompression Sickness Database (unpublished). There were 1,031 exposures from 49 tests to assess DCS and 903 exposures from 42 tests to assess VGE and Grade IV VGE; 7 tests were long exposures ≥ 12 hours to 10.2 psia as part of a staged denitrogenation protocol and no VGE monitoring was performed. The relationships between the 3 outcomes through time is evident in Fig.2; for example, the rate of change seems unique to each outcome but they all plateau at about 4 hours of elapsed time.

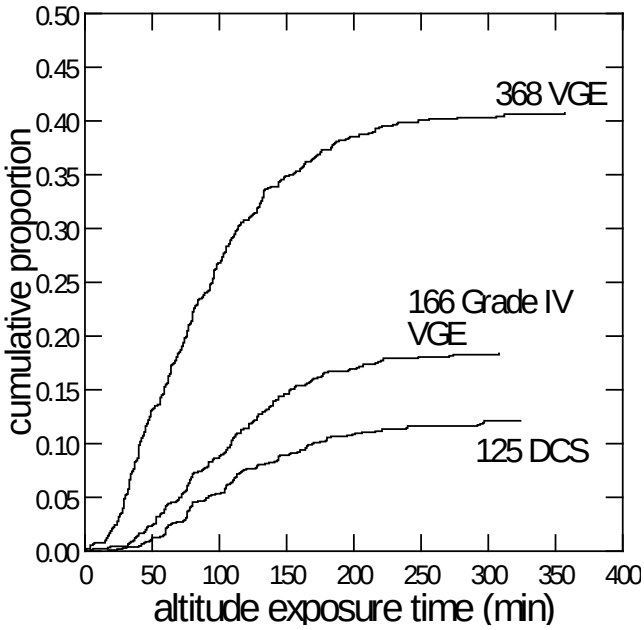

Fig. 2. Cumulative proportion of failure times for any VGE and Grade IV VGE detected in the pulmonary artery and reported DCS symptoms.

Table 1 shows the subject participation history. 577 individuals participated in 1,031 exposures from 1983–2016. 39% of all exposures were with only 1 subject, therefore; 61% of all exposures were with subjects that participated 2 or more times.

Table 1. Subject Participation History

Exposures	Subjects	Cumulative Total	Cumulative Percent
1	402	402	39
2	89	580	56
3	33	679	66
4	21	763	74
5	9	808	78
6	3	826	80
7	5	861	83
8	4	893	86
9	0	893	86
10	3	923	89
11	2	945	91
12	0	945	91
13	1	958	93
14	3	1000	97
15	1	1015	98
16	1	1031	100

Table 2 lists the 49 tests, details of each test (e.g., P2, TR, duration, demographics), the observed incidence of DCS, VGE, and Grade IV VGE for each test, and the estimated probability for each using the regressions described below. There were 577 subjects (431 men and 146 women) that participated in 49 tests covering 1,031 hypobaric exposures (834 exposures with men and 192 exposures with women). Abbreviations for column headings are provided in the Methods. The exact prebreathe details and a description of the DCS and VGE outcomes for all tests except Nuc-1 and Nuc-3 are available (Conkin *et al.* 2014). A description of Nuc-1 and Nuc-3 are also available (Conkin *et al.* 2017).

Table 2. Summary of NASA DCS, VGE, and Grade IV VGE Results with Mean TR

Test	P2 (psia)	time (h)	sample m	f	mean AGE	mean BMI	mean TR	REP	AMB	DCS (%)	P (DCS) as % **	VGE (%)	P (VGE) as %	G IV VGE %	P (G IV VGE)
1a	4.3	3	11	0	34.5	23.9	1.75	0	1	36.3	21.9	63.6	60.3	36.3	36.7
1b	4.3	3	13	0	32.3	23.3	1.81	0	1	23.0	29.1	84.6	64.2	53.8	39.7
1b10.2	10.2	12	13	0	32.3	23.3	1.13	0	1	0	4.7	n/a	36.4	n/a	16.0
1c	4.3	3	12	0	32.0	24.0	1.64	0	1	33.3	12.7	58.3	48.3	50.0	24.3
1c10.2	10.2	12	12	0	32.0	24.1	1.13	0	1	0	4.4	n/a	36.1	n/a	15.7
1d	4.3	3	3	0	39.6	23.5	1.70	0	1	66.6	17.4	100	59.5	66.6	37.6
1d10.2	10.2	18	3	0	39.6	23.5	1.13	0	1	0	7.6	n/a	52.5	n/a	30.9
2a	4.3	4	23	0	31.6	23.7	1.69	0	1	30.4	22.5	65.2	60.3	34.8	35.4
2b	4.3	4	22	0	31.5	23.5	1.74	0	1	27.3†	27.7	45.4	64.1	31.8	39.5
2b10.2	10.2	12	22	0	31.5	23.5	1.13	0	1	0	4.5	n/a	35.7	n/a	15.4
3a	4.3	6	28	0	31.0	24.9	1.60	0	1	21.4	20.9	46.4	61.6	39.3	36.6
3b	4.3	6	35	0	30.1	24.8	1.67	0	1	22.8	28.8	57.1	67.2	23.0	42.7
3b10.2	10.2	12	35	0	30.1	24.8	1.01	0	1	0	2.0	n/a	25.0	n/a	9.3
3c	4.3	6	14	0	32.5	25.2	1.35	0	1	21.4	5.6	35.7	39.0	7.1	18.0
3d	4.3	6	12	0	28.5	24.8	1.40	0	1	16.6	7.7	41.6	40.9	16.6	18.0
4a	4.3	3	12	0	30.1	24.2	1.67	0	1	8.3	14.5	58.3	49.7	25.0	25.0
4a10.2	10.2	12	12	0	30.1	24.2	1.01	0	1	0	2.1	n/a	24.9	n/a	9.3
4b	4.3	3	12	0	30.1	24.2	1.10	0	1	0	0.6	16.6	9.8	8.3	2.9
4c	4.3	3	12	0	30.1	24.2	1.36	0	1	0	2.6	33.3	22.6	6.3	8.1
4d	4.3	3	12	0	30.1	24.2	0.94	0	1	0	0.2	0	5.4	0	1.4
4e	4.3	3	12	0	30.1	24.2	1.34	0	1	0	2.3	33.3	21.3	8.3	7.5
4f	4.3	3	12	0	30.1	24.2	0.92	0	1	0	0.2	0	5.2	0	1.4
5a	4.3	6	19	19	31.5	22.7	1.31	0	1	10.5	5.4	29.0	28.7	10.6	11.3
5b	4.3	6	11	0	32.0	24.5	1.04	0	1	0	1.0	0	15.8	0	5.3
6	6.0	6	15	14	32.9	22.4	1.22	0	1	3.4	3.5	10.3	23.7	0	9.2
610.2	10.2	24	15	14	32.9	22.4	0.89	0	1	0	3.0	n/a	26.8	n/a	10.9
7a	6.5	3	11	0	28.2	24.1	1.78	0	1	36.3††	24.1	72.7	58.0	54.5	31.7
7b	6.5	3	11	0	28.2	24.6	1.78	0	1	18.2	23.2	72.7	58.1	27.2	31.8
8a	6.5	3	29	11	32.4	24.1	1.78	0	1	17.5	24.0	50.0	57.6	32.5	33.1
8b	6.5	3	30	11	32.6	24.1	1.78	0	1	24.4†	24.0	53.6	57.7	41.4	33.4
9a	6.5	3	15	9	32.1	25.2	1.78	0	1	4.1	22.2	50.0	55.9	29.1	31.6
9b	6.5	3	14	9	33.8	25.5	1.78	0	0	8.7†	7.7	26.1	34.3	4.3	9.3
9c	4.3	3	9	2	34.8	25.2	1.66	0	1	27.3	12.7	45.4	49.6	36.3	26.1
9d	4.3	3	6	1	36.4	24.5	1.66	0	0	0	9.4	28.5	28.8	0	7.0
9e	4.3	3	7	0	34.5	24.7	1.46	0	0	0	1.3*	28.5	16.1	0	3.1
10	10.11	3	14	5	31.7	24.5	1.22	0	0	5.2	0.3	31.6	5.7	15.8	0.8
11a	4.3	4	16	12	33.2	24.0	1.85	0	0	10.7	17.9	25.0	47.2	14.3	14.7
11b	6.5	2	1	3	39.5	21.1	1.75	0	1	0	17.0	25.0	43.5	0	21.9
P I	4.3	4	35	14	29.4	24.1	1.87	1	0	18.3	9.8*	49.0	35.9	4.0	9.0
P II	4.3	4	38	12	32.2	24.7	1.85	1	0	0	8.8*	30.0	37.2	6.0	10.3
P III	4.3	4	8	2	29.4	25.2	1.92	1	0	20.0†	11.5*	20.0	41.5	10.0	11.3

P IV	4.3	4	50	15	30.4	24.7	1.90	1	0	12.3	11.0*	40.0	40.1	13.8	11.1
V-1	4.3	4	7	3	31.2	23.4	1.99	0	0	30.0	34.5*	60.0	60.5	20.0	23.7
V-2	4.3	4	2	2	42.0	25.1	2.02	0	0	25.0†	35.0*	100	68.3	50.0	34.9
V-3	4.3	4	39	11	36.9	25.1	1.86	0	0	14.0	17.1*	50.0	53.3	10.0	20.0
V-4	4.3	4	4	3	31.1	22.6	1.75	0	0	42.8	11.9*	42.8	36.2	14.3	9.2
V-5	4.3	4	38	11	32.1	24.5	1.73	1	0	4.1	4.4*	29.1	27.4	16.6	6.5
Nuc-1	4.3	4	16	5	36.4	24.2	1.85	1	1	20.0#	23.8*	61.9	62.5	28.5	39.8
Nuc-3	4.3	4	32	9	36.0	24.1	1.85	1	0	4.8	8.7*	26.8	39.6	9.7	12.0

P2 is the ambient pressure in the hypobaric chamber, n/a is not applicable because monitoring for VGE was not performed, † 1 case was classified as Type II DCS, †† 2 were classified as Type II DCS. *prebreathe included prescribed exercise, all others were resting during prebreathe. # 1 case of left ventricular gas emboli in Nuc-1 was removed early so total count for %DCS = 20. DCS %, VGE %, and G IV VGE % are the observed group incidence. **P(DCS $T < t$), P(VGE $T < t$), and P(G IV VGE $T < t$) are probabilities for the exposures, where t is the exposure time of the test from column 3 and in this case $T = t$. For example, P(DCS) as % (column 11) = P(DCS < 3) × 100 = 21.9.

Table 3 summarizes the regression results for DCS, VGE, and Grade IV VGE for the full and nested model that include TR. We rejected an explanatory variable if the *P*-value was > 0.05. $\beta_{(1)}$ (scale) and $\beta_{(2)}$ (location) are estimated parameters specific to the log-logistic survival model, SE is standard error of the parameter estimate. A negative sign on the estimate indicates a greater probability of the event for a larger value of the explanatory variable.

Table 3. Log-logistic Survival Results with TR as Decompression Dose

DCS 125 in 1,031	**Full Model**			**Step-wise Nested Model** (threshold=0.05)		
Parameter	Estimate	SE	*P*-value	Estimate	SE	*P*-value
$\beta_{(1)}$	0.7481	0.0613	<0.001	0.750	0.0616	<0.001
$\beta_{(2)}$	9.5258	1.135	<0.001	9.177	1.099	<0.001
AGE	-0.0164	0.0092	0.075	-	-	-
SEX	-0.1097	0.207	0.596	-	-	-
BMI	0.0754	0.0312	0.0156	0.0647	0.0280	0.021
TR	-4.403	0.482	<0.001	-4.418	0.484	<0.001
AMB	-0.925	0.209	<0.001	-0.911	0.208	<0.001
REP	0.574	0.214	0.007	0.593	0.216	0.006

VGE 368 in 903	**Full Model**			**Step-wise Nested Model** (threshold=0.05)		
Parameter	Estimate	SE	*P*-value	Estimate	SE	*P*-value
$\beta_{(1)}$	0.939	0.043	<0.001	0.941	0.0434	<0.001
$\beta_{(2)}$	8.691	0.914	<0.001	9.999	0.787	<0.001
AGE	-0.031	0.0078	<0.001	-0.0298	0.0077	<0.001
SEX	-0.636	0.1818	<0.001	-0.5133	0.1673	0.002
BMI	0.043	0.0247	0.076	-	-	-
TR	-3.695	0.3905	<0.001	-3.660	0.390	<0.001
AMB	-0.882	0.175	<0.001	-0.9095	0.175	<0.001
REP	0.482	0.174	0.006	0.471	0.175	0.007

GIV VGE 166 in 903	Full Model			Step-wise Nested Model (threshold=0.05)		
Parameter	Estimate	SE	*P*-value	Estimate	SE	*P*-value
$\beta_{(1)}$	0.845	0.060	<0.001	0.845	0.0599	<0.001
$\beta_{(2)}$	11.531	1.293	<0.001	11.403	1.136	<0.001
AGE	-0.043	0.0095	<0.001	-0.0435	0.0094	<0.001
SEX	-0.517	0.2446	0.034	-0.5369	0.226	0.019
BMI	-0.0064	0.0304	0.83	-	-	-
TR	-3.631	0.530	<0.001	-3.635	0.530	<0.001
AMB	-1.423	0.229	<0.001	-1.418	0.2276	<0.001
REP	0.476	0.227	0.036	0.4778	0.2273	0.032

Equation 4 is the log-logistic survival model for DCS.

$$P(\text{DCS } T< t) = 1 / (1+\exp(-(\ln(t) - 9.177 + 4.418\times TR + 0.911\times AMB - 0.0647\times BMI - 0.593\times REP) / 0.750)), \quad \text{Eq. 4}$$

where P(DCS $T < t$) is the probability that survival time T for DCS is $< t$, that DCS will be observed in the interval between 0 and t ($0 \leq T < t$), t is in hours from start of exposure at the test pressure (P2), TR is tissue ratio [$P_{tis}N_2$/P2] at the start of the hypobaric exposure, ambulation status (AMB) is either 1 or 0, which indicates that ambulation is part of the physical activity in the hypobaric chamber, BMI is body mass index, the ratio of mass in kg divided by height squared in meters, and REP is the presence (1) or absence (0) of a brief depressurization to 10.2 psia followed by a repressurization to 14.7 psia as part of a prebreathe before a final depressurization to 4.3 psia. Eq. 4 is based on 1,031 exposures (834 male-exposures and 197 female-exposures) in 49 unique protocols with 125 cases of DCS taken from the NASA Hypobaric Decompression Sickness Database.

Figure 3 shows the observed group incidence of DCS versus the estimated P(DCS $T < t$) for t shown in Table 2 column 3 and the other explanatory variables in each row. Figure 3 is a visual assessment of goodness-of-fit of the regression model. A perfect description of the data by the regression model would show the observed incidence for all 49 tests aligned along the identity line.

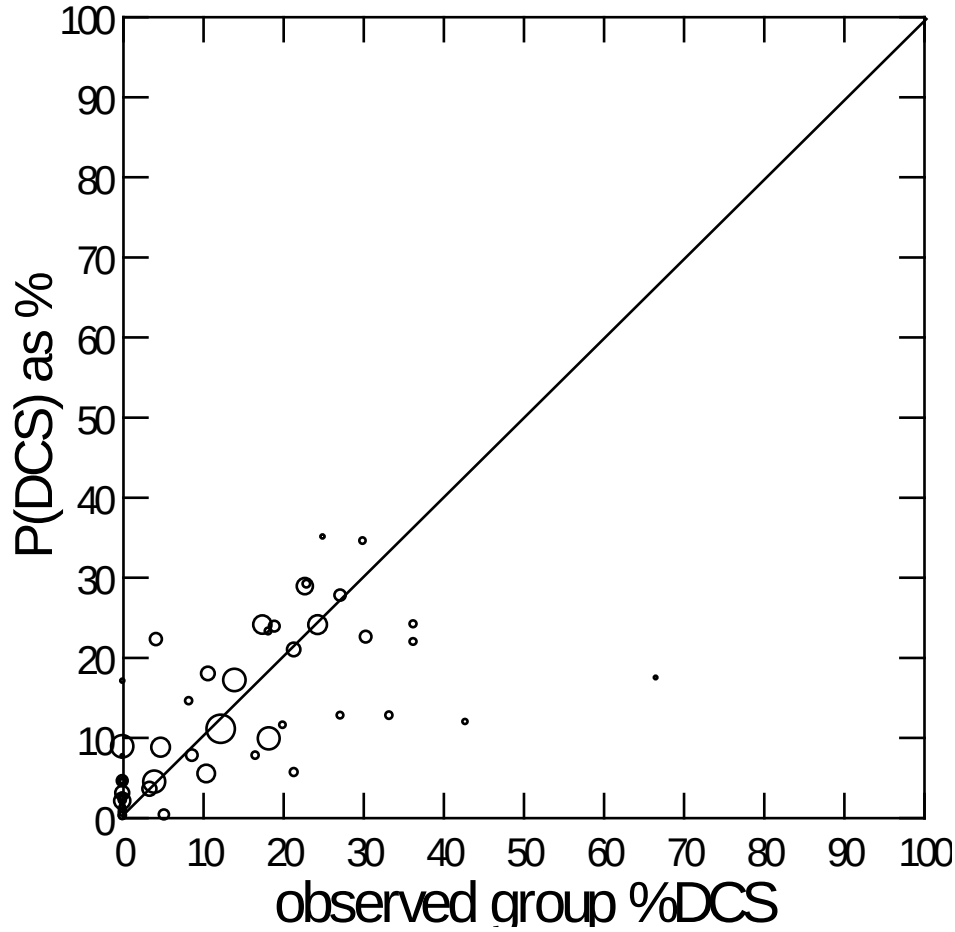

Fig. 3. Observed versus 100 × P(DCS $T < t$), where t is defined in Table 2 column 3 (labeled P(DCS) as %), for each test duration based on 125 cases in 1,031 exposures from 49 tests using 577 subjects. Area of circles reflects sample size from 49 tests, smallest group size was 3 and largest was 65.

Figure 4 summarizes the P(DCS $T < t$) and its associated 95% confidence interval (CI) at t = 6 hours with a TR of 1.70 and 1.30. Other covariates were: BMI of 24 kg/m^2, ambulates as part of physical activity at 4.3 psia, and there was no brief depressurization / repressurization to 10.2 psia as part of prebreathe, i.e., REP = 0.

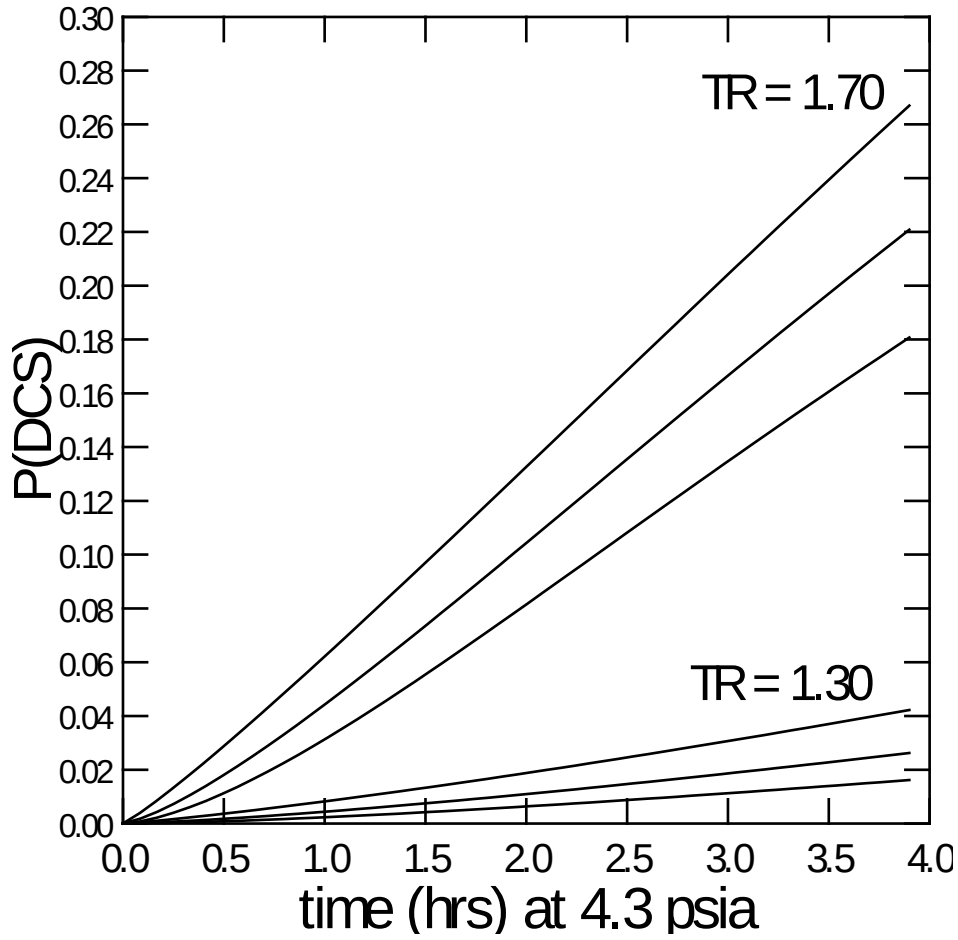

Fig. 4. Estimated P(DCS $T < t$), and 95% CI, increases with greater TR as time at 4.3 psia increases given that the person is ambulatory as part of the physical activity at 4.3 psia. See text for other details about the explanatory variables.

The association between Body Mass Index (BMI) and time to DCS is now explored in some detail. A positive value of the BMI coefficient (0.064) in Table 3 means that as the variable increases in magnitude the P(DCS $T < t$) decreases. A unit increase in BMI is associated with an increase in DCS survival by a factor of exp(0.064) = 1.07 [95% Wald CI: 1.01 to 1.13] when holding all other covariates constant. We have no mechanistic (cause-and-effect) rationale why an increase in BMI is associated with a decrease in P(DCS $T < t$). There may be some model misspecification due to lack of controlling for key variables or for excluded key interaction terms. Figure 5 shows the relationship between BMI and body fat as a percent of body mass by gender. Body fat percent was often assessed by 3- or 7-site skin fold measurements or, in a few cases, by underwater weighing. Women have a greater percentage of body mass as fat than men do for the same BMI. Figure 6 shows the magnitude of change in P(DCS $T < t$) for a specific case where BMI was evaluated across a wide range.

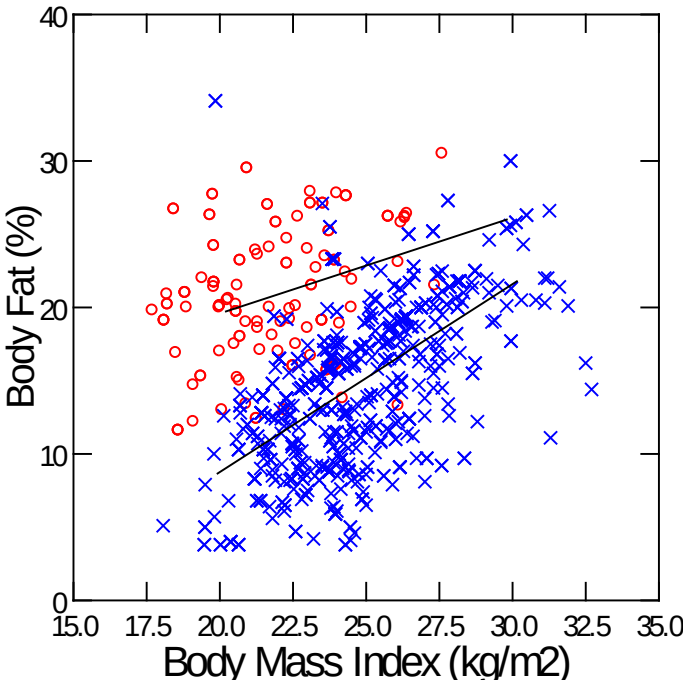

Fig. 5. Relationship between BMI and body fat as a percentage of body mass by gender. General trends (lines) were estimated with linear least-squares regressions in subgroups (women = red circles and men = blue crosses).

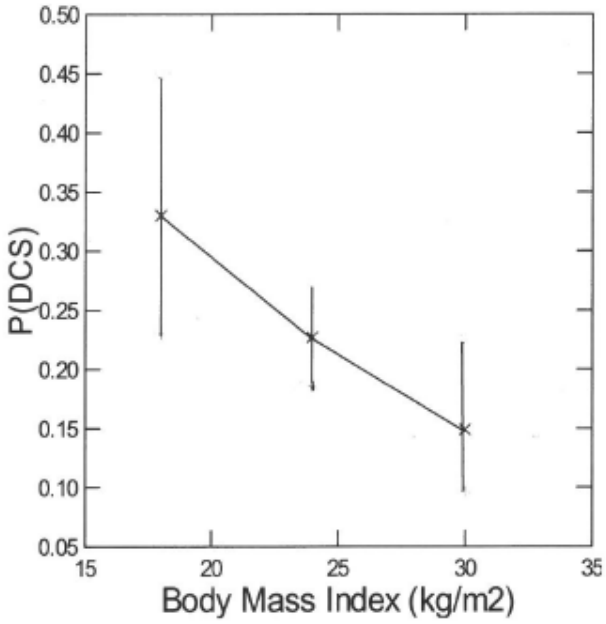

Fig. 6. Estimated P(DCS $T < t$) decreases over a large range of increasing BMI. Estimates based on Eq. 4, among subjects with a TR of 1.70, ambulation at 4.3 psia for 4 hours, and there was no brief depressurization / repressurization to 10.2 psia as part of prebreathe.

We also evaluated our interval-censored survival data for VGE and Grade IV VGE. Equation 5 estimates a P(VGE $T < t$) and is based on 903 exposures with 368 cases of any VGE grade, including Grade IV, first detected with our precordial Doppler bubble monitor.

$$P(\text{VGE } T< t) = 1 / (1+\exp(-(\ln(t) - 9.559 + 0.0298\times\text{AGE} + 3.66\times\text{TR} + 0.513\times\text{SEX} + 0.909\times\text{AMB} - 0.471\times\text{REP}) / 0.941)), \quad \text{Eq. 5}$$

where SEX = 1 for male and 0 for female, AGE is in years, and other explanatory variables as defined earlier.

Figure 7 shows the observed group incidence of VGE versus estimated P(VGE $T < t$) for each test duration from the results in Table 2 where $T = t$ from column 3 and the other explanatory variables in each row.

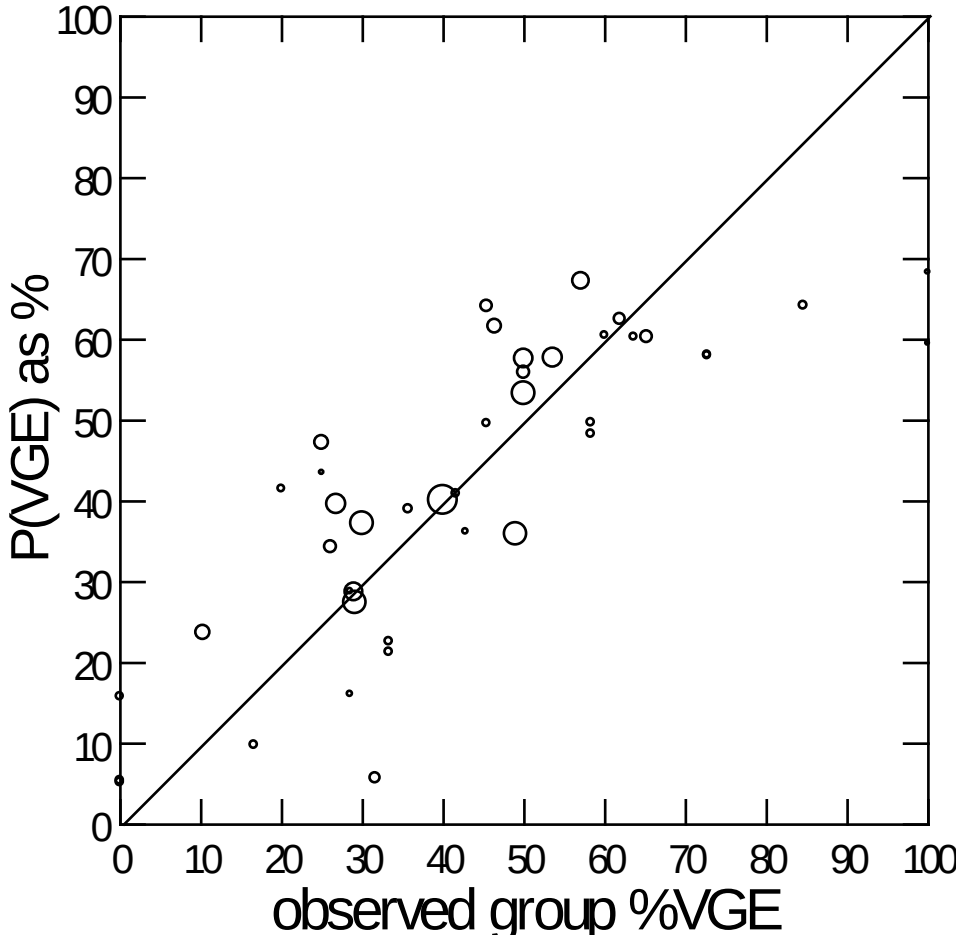

Fig. 7. Observed versus estimated P(VGE $T < t$) based on 368 cases in 903 exposures from 42 tests using 577 subjects; 7 tests were long exposures ≥ 12 hours to 10.2 psia as part of a staged denitrogenation protocol and no VGE monitoring was performed. Area of circles reflects sample size from 42 tests, smallest group size was 3 and largest was 65.

Equation 6 estimates P(Grade IV VGE $T < t$) and is based on 903 exposures with 166 cases of Grade IV VGE first detected with our precordial Doppler bubble monitor.

$$P(\text{Grade IV VGE } T < t) = 1 / (1+\exp(-(\ln(t) - 11.403 + 0.0435\times\text{AGE} + 3.635\times\text{TR} + 0.537\times\text{SEX} + 1.418\times\text{AMB} - 0.477\times\text{REP}) / 0.845)). \quad \text{Eq. 6}$$

Figure 8 shows the observed group incidence of Grade IV VGE versus estimated P(Grade IV VGE $T < t$) for each test duration from the results in Table 2 where $T = t$ from column 3 and the other explanatory variables in each row.

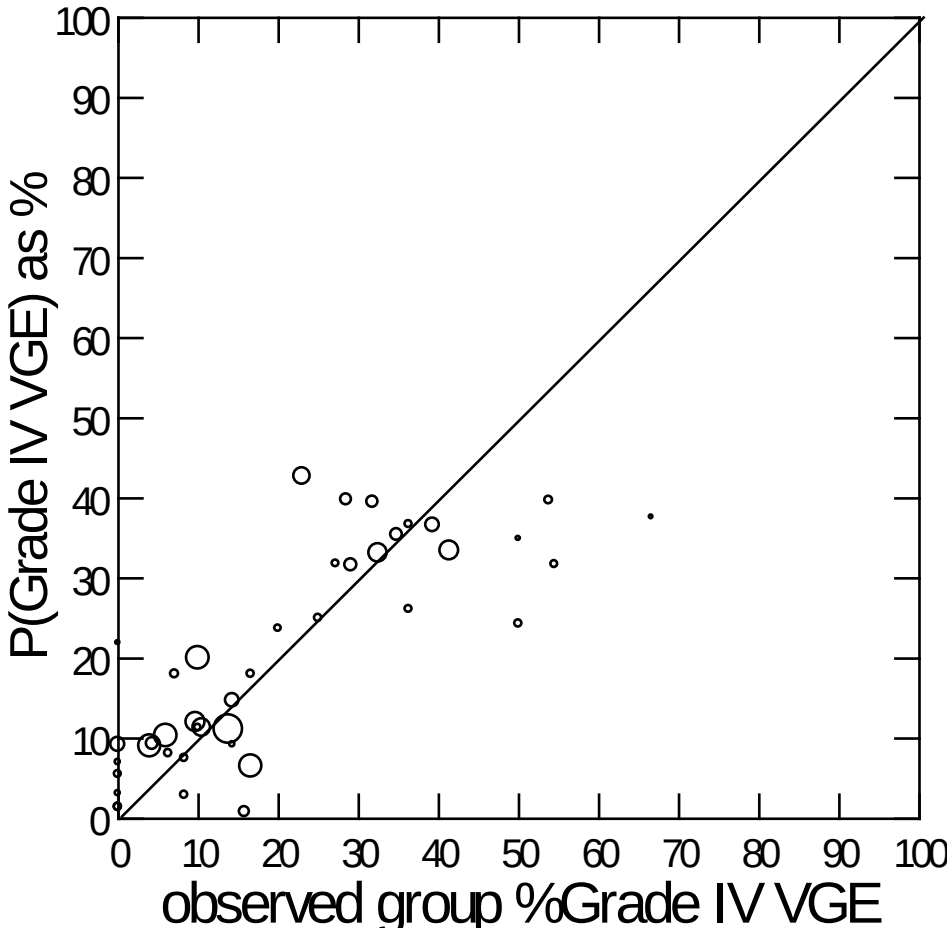

Fig. 8. Observed versus estimated P(Grade IV VGE $T < t$) based on 166 cases in 903 exposures from 42 tests using 577 subjects; 7 tests were long exposures ≥ 12 hours to 10.2 psia as part of a staged denitrogenation protocol and no VGE monitoring was performed. Area of circles reflects sample size from 42 tests, smallest group size was 3 and largest was 65.

4.0 THE SPECIAL CASE OF THE EXPLORATION ATMOSPHERE

The Human Health and Performance Directorate at NASA JSC is charged with maintaining the health of the astronaut corps during all phases of training, flight, and re-adaptation. Future astronauts participating in Exploration-Class EVA must not be burdened with undue risk of DCS. Hypobaric DCS can range from Type I (pain-only) symptoms that modify or terminate an EVA to symptoms that threaten the health and safety of the astronaut, lumped into a category of Type II DCS. Standard-of-care treatment for DCS is not practical at remote locations of EVAs. Therefore, mitigation of risk as opposed to treatment of symptoms as a solution is a primary goal. Tissue denitrogenation before exposure to low pressure in a space suit is effective to reduce DCS risk. NASA has employed several prebreathe strategies over 50 years to minimize DCS risk during EVA: resting 100% O_2 prebreathe while in a spacecraft or suit, staged denitrogenation, and mild exercise to accelerate denitrogenation while breathing 100% O_2. All have proven effective but at various costs of complexity to implement, crew time to prepare, and utilization of limited O_2 resources.

As humans venture into the solar system, they must function with more autonomy. The exploration atmosphere (EA) prebreathe protocol is an engineering solution to eliminate DCS as an operational and medical concern and to free the crew from the overhead of conducting a lengthy in-suit prebreathe. Current prebreathe options require the crew to flawlessly execute the protocol with significant support from Mission Control personnel. Protocols available for the International Space Station are considered "just in time" mitigations in that you complete the minimum prebreathe just in time before the EVA. This approach has more uncertainty as to its efficacy than an alternative approach. A better approach is to live in an environment where tissue N_2 tension is reduced to a point where it is very near or even lower than the suit pressure. In this way, you minimize with greater certainty the tissue N_2 supersaturation during the EVA. The challenge with this approach is to reduce atmospheric PN_2 without increasing atmospheric PO_2 to minimize the risk of flammability and medical concerns with hyperoxia. The approach is to reduce ambient pressure in the habitat while increasing the O_2 concentration to achieve as low a PN_2 while minimizing hypoxia and the risk of fire. After much analysis and debate among medical, science, materials, and operations experts during 2 sessions of the Exploration Atmospheres Working Group (2006 and 2012) a candidate atmosphere was selected.

The EA prebreathe involves reaching equilibration with the ambient PN_2 of 5.4 psia before EVA at 4.3 psia by living at 8.2 psia while breathing 34% O_2 – 66% N_2. The resulting inspired O_2 partial pressure (P_IO_2) of 128 mmHg is mildly hypoxic relative to sea level P_IO_2 of 149 mmHg. A P_IO_2 of 128 mmHg is approximately equivalent to breathing air at 4,000 feet altitude. As such, the EA is classified as mild hypoxia. A 2015 review of the EA by a research and clinical advisory panel concluded that there was nothing inherently problematic about living and working at a P_IO_2 of 128 mmHg in otherwise healthy adults. However, there was uncertainty if mild hypoxia would have a positive or negative synergy with physiological adaptation to microgravity or even reduced gravity on a planetary surface. There was uncertainty if a hypoxic P_IO_2 dose of 128 mmHg while breathing 34% O_2 at 8.2 psia (15,600 feet) was truly equivalent to the same hypoxic P_IO_2 dose of 128 mmHg while breathing air at 4,000 feet.

The EA protocol is acceptable once validated through human testing if it meets or exceeds the current acceptable risk of DCS and Grade IV VGE for future planetary EVA:

- Accept protocol if Type I DCS is ≤ 15% with 95% confidence and if Grade IV VGE ≤ 20% with 95% confidence,
- Reject protocol if Type I DCS is > 15% with 70% confidence or if Grade IV VGE > 20% with 70% confidence, and
- Reject protocol if Type II DCS is diagnosed.

We apply Eqs. 3, 4, 5, and 6 to the EA prebreathe protocol. All 8 participants perform a 3-hour 100% O_2 mask prebreathe before a 1-hour depress from 14.7 psia to 8.2 psia. The masks are removed at 8.2 psia once 34% O_2 and 66% N_2 is established. The participants will then equilibrate to a PN_2 of 5.4 psia and the mildly hypoxic P_IO_2 of 128 mmHg in the atmosphere for 48 hours. Following the equilibration period, each of 6 subjects will don masks and breathe 85% O_2 during a 15-minute depressurization to 4.3 psia. The 2 DTs will don masks with 100% O_2 30 minutes before depressurization to 4.3 psia. The EVA simulation for 6 subjects involves 6 hours of prescribed activity that imposes repetitive isometric and isotonic contractions against loads in the upper and lower body under a simulated ambulatory planetary scenario.

Table 4 details the major times and events associated with the EA prebreathe protocol. Each DT performs noninvasive Doppler bubble monitoring for VGE in the pulmonary artery on each of 3 subjects for 5 minutes at 15-minute intervals during the 4.3 psia exposure. A 15-minute repressurization will return all subjects and DTs to 8.2 psia and the cycle will be repeated 4 additional times with 41.5 hours between the starting times of simulated EVAs.

Table 4. Times and Events of Exploration Atmosphere Prebreathe Protocol

Day	Elapsed time (min)	Event Time (hr:min)	Computed tissue N_2 (psia)* and resulting tissue ratio	Computed BGI**	Activity
0	-1140	13:00			Subjects and DTs report to chamber, some pre-test data collection, preflight physical, systems review, dinner, and first sleep.
1	0	08:00			Finish breakfast, start 3 hr PB
1	180	11:00			End 3 hour PB, depress to 8.2 psia
1	240	12:00	7.3, 0.89	1.00	Start 48 hour equilibration
2					48 hour rest plus prep for EVA 1 Hypoxia data collection
3	3120	12:00	5.41	1.00	Start 15 minute depress to 4.3 psia
3	3135	12:15	5.29, 1.23	1.07	@ 4.3 psia, continue EVA 360 minutes
3	3495	18:15		25.0	End 6 hour EVA and repress to 8.2 psia
3	3510	18:30	2.91	20.0	At 8.2 psia and start 41:30 rest
4					Rest and prep for EVA 2
5	6000	12:00		1.00	Start 15 minute depress to 4.3 psia
5	6015	12:15	5.26, 1.22	1.07	@ 4.3 psia, continue EVA 360 minutes
5	6375	18:15		24.6	End 6 hour EVA and repress to 8.2 psia
5	6390	18:30	2.90	19.6	At 8.2 psia and start 41:30 rest
6					Rest and prep for EVA 3
7	8880	12:00		1.00	Start 15 minute depress to 4.3 psia
7	8895	12:15	5.26, 1.22	1.07	@ 4.3 psia, continue EVA 360 minutes
7	9255	18:15		24.6	End 6 hour EVA and repress to 8.2 psia
7	9270	18:30	2.90	19.6	At 8.2 psia and start 41:30 rest
8					Rest and prep for EVA 4
9	11760	12:00		1.00	Start 15 minute depress to 4.3 psia
9	11775	12:15	5.26, 1.22	1.07	@ 4.3 psia, continue EVA 360 minutes
9	12135	18:15		24.6	End 6 hour EVA and repress to 8.2 psia
9	12150	18:30		19.6	At 8.2 psia and start 41:30 rest
10					Rest and prep for EVA 5
11	14640	12:00		1.00	Start 15 minute depress to 4.3 psia
11	14655	12:15	5.26, 1.22	1.07	@ 4.3 psia, continue EVA 360 minutes
11	15015	18:15		24.6	End 6 hour EVA and repress to 8.2 psia
11	15030	18:30		19.6	At 8.2 psia
11	15045	18:45		14.7	At 14.7 psia, end test on air
11	15165 252 hr : 45 min	20:45		2.9	2 hours at 14.7 psia on air

*computation based on 360-minute half-time

** Bubble Growth Index (BGI) is the ratio of final computed bubble radius to an initial radius of 3 microns for preformed micronuclei (see Appendix B for details about BGI as decompression dose)

Figure 9 shows the computed BGI from 5 repeated EVAs after prebreathe, based on a 360-minute half-time theoretical tissue compartment and assuming EVAs are performed with 85% O_2.

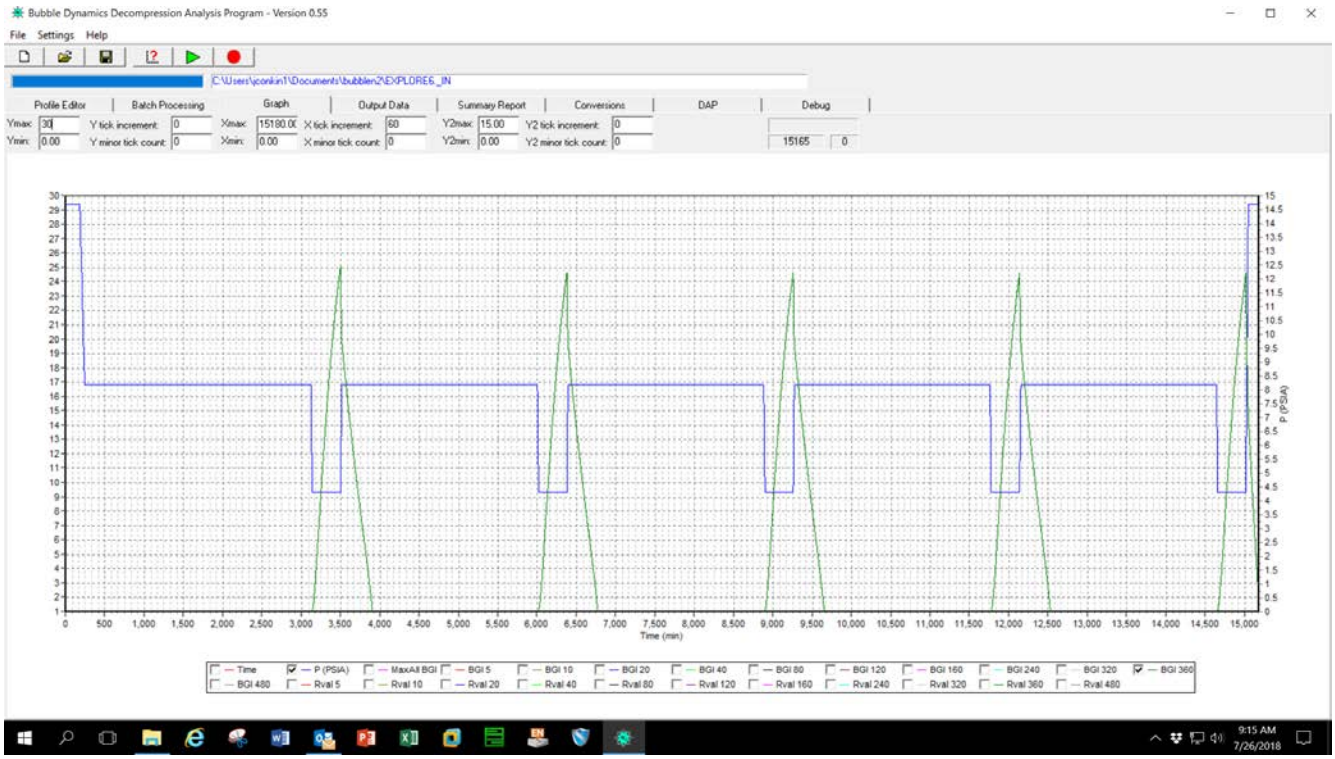

Fig. 9. Computed BGI (left y-axis) through all phases of the proposed testing over 11 days (x-axis). Peak BGI indicates the end of the simulated planetary EVA at 4.3 psia and the beginning of repressurization back to 8.2 psia. The prebreathe is 3 hours of 100% O_2 prebreathe with a 1-hour depressurization to 8.2 psia, then 48 hours breathing 34% O_2 before a 15-minute depress to 4.3 psia on 85% O_2 for a 6-hour EVA, then a 15-minute repress to 8.2 psia for a 41.5-hour interval before start of next depress to 4.3 psia. Maximum BGI is 25 units and maximum TR is 1.23.

$P_{tis}N_2$ from Eq. 3 decreases during the initial exposure to 8.2 psia while breathing a PN_2 of 5.4 psia. Computed $P_{tis}N_2$ decreases during the 6-hour simulated EVA and then increases during the rest interval between EVAs back at 8.2 psia. The computed TR is 1.23 for the first simulated EVA and then 1.22 for the remaining 4 EVAs (see Table 4). A TR of 1.23 indicates very modest decompression stress; for reference, operational EVAs from the Space Shuttle were conducted with a TR of about 1.60. However, EVAs from the Space Shuttle were and ISS are performed under nonambulatory conditions, which reduces the risk of DCS symptoms in the lower body (Conkin & Powell, 2001, Conkin *et al*., 2017).

Application of Eq. 4 estimates a P(DCS $T < t$) of 3.1% (1.8% to 5.2%) for a physically active ambulatory subject with a BMI of 24 and based on computed TR of 1.23 for a t = 6 hour exposure where repressurization to 14.7 psia was not part of a prebreathe before a final depressurization to 4.3 psia. However, the P(DCS) estimate is based on representative EVA activity that is different from what is proposed to validate the EA prebreathe. The type, duration, and intensity of exercise, both mean and particularly peak intensity, will be greater than in our prior testing. It is reported that the highest 1-

minute O_2 consumption rate normalized to body weight during simulated EVA activity showed a high correlation with DCS risk (Webb *et al*. 2010, Conkin *et al*. 2013).

Application of Eq. 5 estimates a P(VGE $T < t$) of 28.0% (21.2% to 36.0%) for a physically active ambulatory male and 18.4% (12.3% to 26.5%) for a female, both at age 32 years and based on a computed TR of 1.23 for a t = 6 hour exposure where repressurization to 14.7 psia was not part of a prebreathe before a final depressurization to 4.3 psia.

Application of Eq. 6 estimates s a P(Grade IV VGE $T < t$) of 11.0% (6.4 to 17.4) for a physically active ambulatory male and 6.0% (3.0 to 12.0) for a female, again both at age 32 years and based on a computed TR of 1.23 for a t = 6-hour exposure where repressurization to 14.7 psia was not part of a prebreathe before a final depressurization to 4.3 psia.

A limitation in our predictions is that extrapolation out of the range in which the data were collected adds uncertainty to our interpretation of the results, as well as our assumption that the models are correct. For example, a majority of the historical exposures were 4 hours in duration (mean of 4 ± 1 hour SD). So extrapolating simulation results to 6 hours overestimates the risk because risk always increases in our log-logistic survival model as time goes to infinity. In reality, the onset of new bubbles past about 4 hours of exposure is uncommon in our conservative protocols (see Fig. 2). So in our examples of 28% VGE and 11% Grade IV VGE after 6 hours in a male, we likely overestimate what will be observed by 6 hours. An alternative is to evaluate the probability after 4 hours with the assumption that no new bubbles will appear in those with no VGE before 4 hours. In this case, we estimate 20% for VGE and 7% for Grade IV VGE in males after a 6-hour exposure. It should be noted that metabolic rates during the proposed planetary EVA simulation will be about twice as high as those associated with the ambulatory data used to parameterize our survival model, which may have the effect of increasing decompression risk compared with model predictions.

5.0 DISCUSSION

The discussion includes information on the location and characterization of Type I DCS symptoms, details that are not captured in the previous regressions. Complete case descriptions for Type I DCS and the 7 cases classified as Type II DCS are available elsewhere (Conkin *et al*. 2014). Figures 10 and 11 summarize the anatomical locations and attributes of 220 symptoms in 119 cases of DCS, extracted from our earlier publication (Conkin *et al.* 2014, 2015). Six cases of DCS from Nuc-1 and Nuc-3, our last 2 tests, are not part of these figures. Figure 10 shows that the lower body (knees and ankles) dominates the location of symptoms, but evolved gas was not restricted to the knees and ankles. The symptom was often described as painful and constant in character (see Fig. 11). Conservative prebreathe protocols and test termination criteria limited our experience with Type II DCS, only 7 cases were observed in 125 cases of DCS in 1,031 exposures.

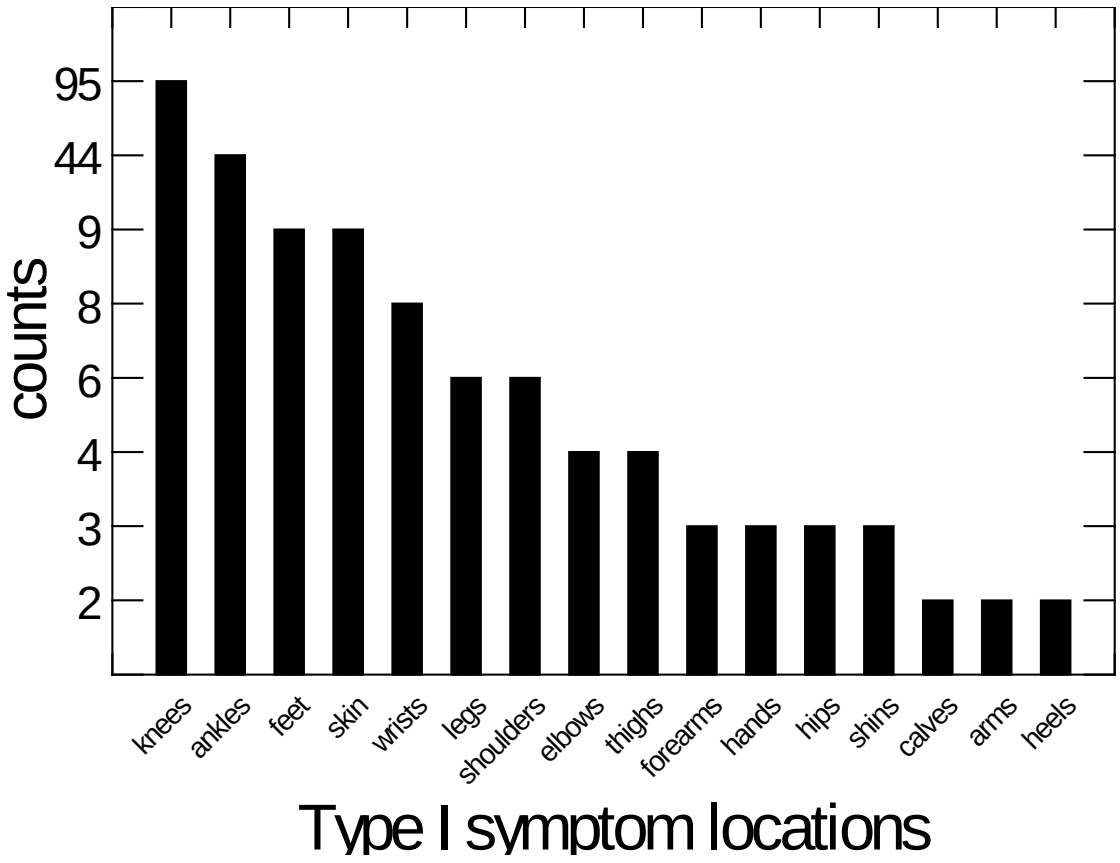

Fig. 10. Anatomical locations of 203 symptoms of Type I DCS in 119 of 125 cases of DCS. Symptoms in toes or fingers were included in feet or hands.

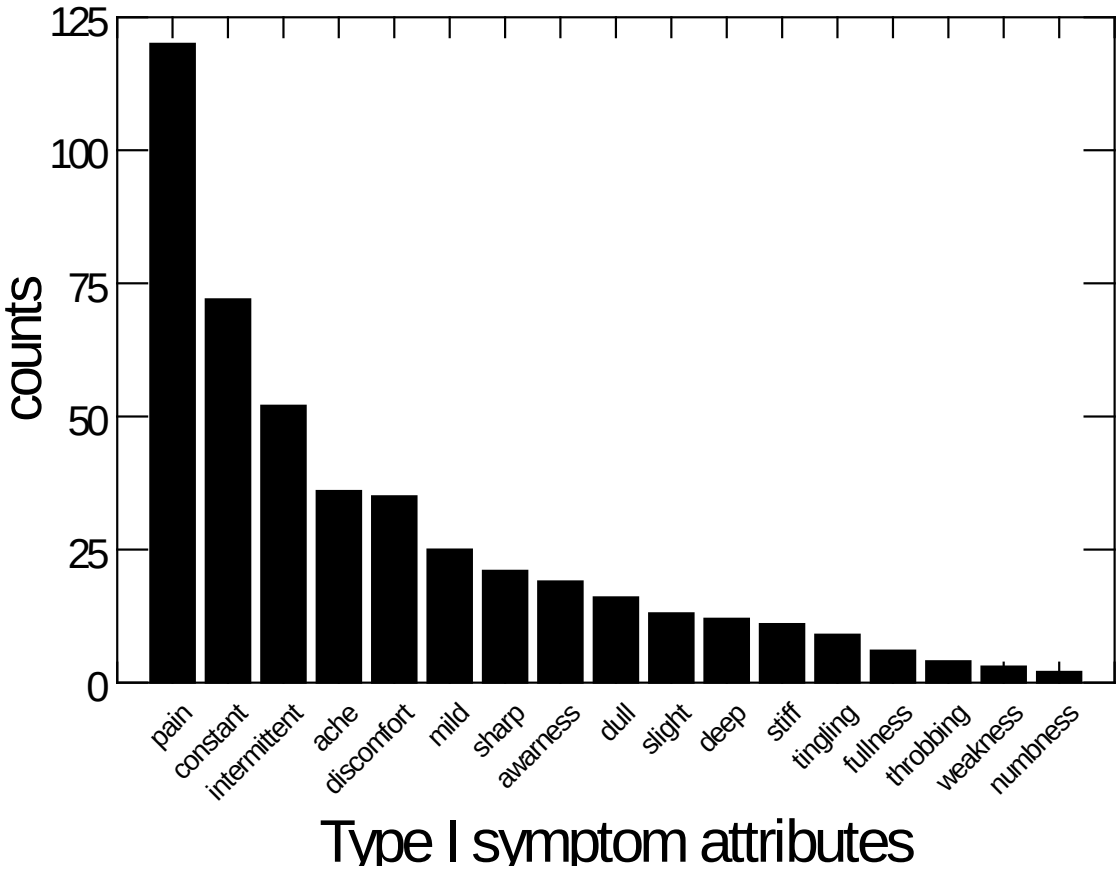

Fig. 11. Counts of 456 symptom attributes in 119 of 125 cases of DCS. Seven of the 9 records for "tingling" symptoms came from 1 subject. The 2 symptoms of numbness were attributed to impaired circulation and not to neurological causes.

5.1 Limitations and Applications

The goal of prebreathe testing by NASA has always been to reduce the risk of DCS and VGE, and not to study DCS *per se*. So our experience with DCS is limited to outcomes from conservative prebreathe protocols. Our regressions are less-applicable to fast depressurizations to low pressure without significant denitrogenation. A limitation in the simulations is that extrapolation out of the range in which the data were collected adds uncertainty to our interpretation of the results. For example, a majority of the historical exposures were 4 hours in duration (mean of 4 ± 1 hour SD). So extrapolating simulation results to 6 hours overestimates the risk because risk always increases in our log-logistic survival model as time goes to infinity. Other approaches such as cure-rate survival models could address this limitation (Thompson *et al*. 2002).

Subjects did volunteer for more than 1 of the 49 tests, but no subject repeated the same test. For example, 402 of 577 subjects participated in only 1 of 49 tests while 89 participated in 2 and 86 participated in 3 or more tests. We had no provision in our analysis to account for multiple participations of 1 subject across different tests; therefore, we assume independence. Other approaches in survival

analysis such as using “robust” standard errors to account for subject clustering could address this limitation. Subjects were not excluded from multiple participations if they had DCS or VGE in a prior test. Confounding and interactions between variables were not evaluated.

Our regressions apply to near square-wave depressurizations where P2 is constant for the duration of the low pressure exposure. Near square-wave depressurization means that the depressurization from sea level pressure to final P2 varied from about 5 to 30 minutes. No tests were done with very long (slow depress rate) or very short (fast depress rate) depressurization rates. TR as decompression dose in applications where P2 varies over short time intervals is not justified. TR based on P2 other than 4.3 psia is not available for most of our data. It is known that the same TR ($P_{tis}N_2/P2$) at a larger P2 and a smaller P2 is not associated with the same incidence of DCS in otherwise identical tests; the P(DCS $T < t$) is greater for the same TR given a smaller P2 than a larger P2 (Chadov & Iseyev 1989, Conkin 1994, Van Liew & Burkard 1995, Conkin *et al*. 1996b, Conkin *et al*. 1998a, Conkin *et al*. 2013). This observation limits our current Eq. 4 regression to applications over a narrow range of P2s between about 4.0 to 5.0 psia. However, future EVAs will be performed in the xEMU pressurized up to 8.0 psia. So for applications at P2 > 5.0 psia, we recommend a log-logistic survival regression for P(DCS) described in 1996 (Conkin *et al*. 1996b). The data consisted of 1075 male exposures that resulted in 211 cases of DCS in 66 hypobaric chamber tests. There were more tests done at different P2s in these data than our data with P2s limited to about 10.2, 6.5, and mostly 4.3 psia. The P(DCS) from that regression (Eq. 7) is 3.0% given a TR of 1.23 for a 4-hour simulated ambulatory EVA at 4.3 psia and 5.5% if the EVA is 6 hours. The P(DCS) described here from Eq. 4 is 1.8% for a 4-hour ambulatory EVA at 4.3 psia and 3.1% for 6 hours, so estimates are low in each case but not the same using 2 different regressions from different sets of data.

Table 5 shows 4 suit pressures and in-suit prebreathe times needed to produce the same P(DCS) for a 4- and then a 6-hour ambulatory EVA using the Eq. 7 regression model described in 1996. These examples demonstrate why Eq. 7 and not Eq. 4 should be applied when P2 is > 5.0 psia.

Table 5. Examples of Suit Pressure and In-suit Prebreathe Time to Achieve the Same P(DCS)

Suit pressure (psia)	In-suit prebreathe on 100% O_2 (min)	Depressurization time on 100% O_2 (min)	TR	P(DCS) @ 4-hr ambulatory* EVA	BGI @ 4 hours	P(DCS) @ 6-hr ambulatory** EVA	BGI @ 6 hours
7.5	25	30	1.39	3.0	16.7	5.5	18.7
6.5†	115	30	1.35	3.0	16.6	5.5	19.0
5.3	245	30	1.29	3.0	16.8	5.5	20.0
4.3	380	30	1.23	3.0	17.0	5.5	22.0

*Planetary ambulatory activity will likely be greater than tested in research protocols.
**P(DCS) for the 6-hour simulated EVA is an extrapolation from data used to parameterize the regression model.
†Testing at 6.5 psia with no prebreathe produced a TR of 1.78. There were 127 exposures from 5 tests: 7a, 7b, 8a, 8b, and 9a. Mean age was 30 years old, mean BMI of 24, and with 75% of exposures as males. Exercise that included ambulation was part of the 3-hour exposures on 100% O_2. There were 24 cases of DCS (19%) and 3 cases were classified as Type II DCS. There were 46 cases of Grade IV VGE (36%).

$$P(\text{DCS } T < t) = 1 - \exp^{(-\text{Dose})} \qquad \text{Eq. 7}$$

$$\text{Dose} = \ln \{1 + [((P_{tis}N_2 + 1.563) / P2) - 1]^{4.366} \times [1 + (1.578 \times \text{EXER})] \times (t \times 0.063)^{1.521}\},$$

where P(DCS $T < t$) is the probability that survival time T for DCS is $< t$, that DCS will be observed in the interval between 0 and t ($0 \leq T < t$), t is in hours from start of exposure at the test pressure (P2), ln is natural log, and EXER is the presence (1) or absence (0) of exercise that included ambulation at P2.

In these evaluations, an additional 30 minutes of denitrogenation is provided during the depressurization from 14.7 psia to the final suit pressure and must be accounted for in Eq. 3. Equation 3 was used to calculate the $P_{tis}N_2$ before the start of the simulated EVA. The 4-hour EVA is associated with 3.0% DCS for each combination of suit pressure and total prebreathe time while the 6-hour EVA is associated with 5.5% DCS. Figure 12 shows results from Table 5.

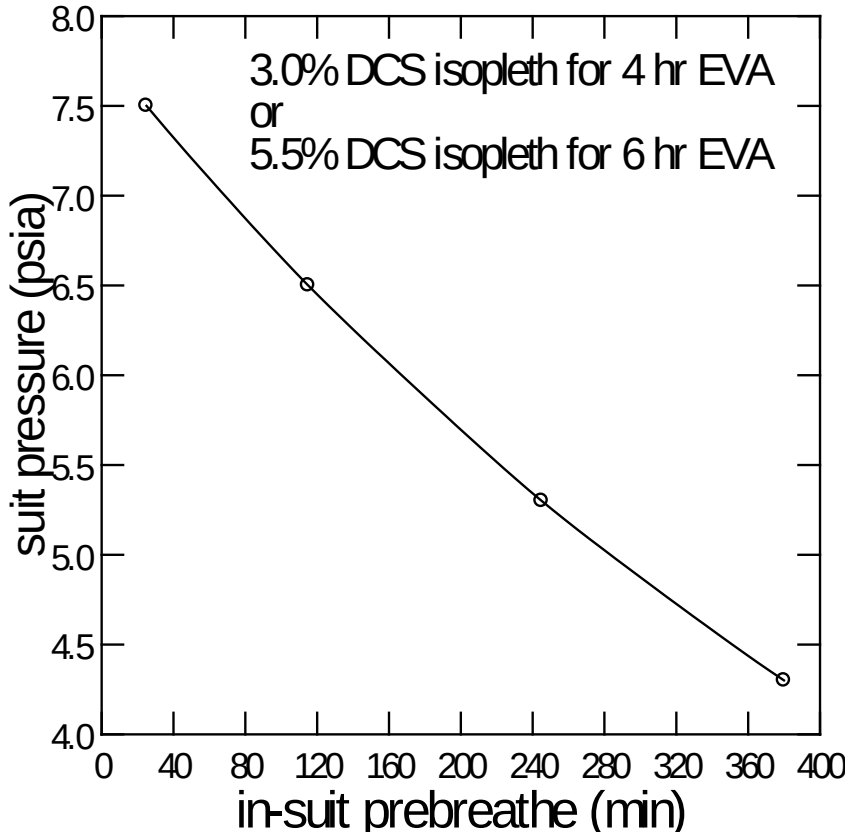

Fig. 12. Relationship between suit pressure and in-suit prebreathe time to achieve P(DCS) isopleths after 4 and 6 hours of simulated ambulatory EVA. Note: you must add 30 minutes to the in-suit prebreathe time to account for the additional prebreathe on going from 14.7 psia to final suit pressure.

Notice that the simple TR in Table 5 is not the same at each suit pressure; it must decrease as suit pressure decreases to provide for the same P(DCS). The reason for this is discussed in greater detail elsewhere (Van Liew & Burkard 1995, Conkin *et al*. 1996b, Conkin *et al*. 1998a, Conkin *et al*. 2013)

and has to do, in part, with the contribution of the constant metabolic gas partial pressure in the gas phase to enhance the tissue-to-bubble N_2 gradient at different P2s. Van Liew & Burkard say, "*The TR is not closely related to bubble size; that is when two different decompressions have the same TR, metabolic gases cause bubbles to grow larger at lower hypobaric pressures. We conclude that the constancy of partial pressures of metabolic gases, unimportant in hyperbaric decompressions, affects bubble size in hypobaric decompressions in inverse relation to the exposure pressure.*" Now the Tissue Bubble Dynamics Model (TBDM) (Gernhardt 1991) includes a constant metabolic gas partial pressure in bubbles that form at different P2s. Notice in Table 5 that the 3.0% DCS isopleth has a BGI of about 17 at 4 hours and about 20 at 6 hours for all suit pressures. The conclusion is that Eq. 7, which includes a fitted term that approximates the metabolic gas modification of the simple TR, is in reasonable accord with the BGI results, at least in these simple simulations. Our regression described as Eq. 4 would not provide a P(DCS) isopleth as does Eq. 7 for a 4- or 6-hour simulated EVA given the TRs from 1.39 to 1.23 seen in Table 5. So we recommend Eq. 7 to provide P(DCS $T < t$) at suit pressures > 5.0 psia. An alternative is to use the time-dependent BGI as decompression dose if P2 is not 4.3 psia even though the goodness of fit of BGI in our data is less than for TR (see Appendix B). In this case, a BGI of about 17 was associated with a 3.0% DCS isopleth after 4 hours from Eq. 7 while a BGI of about 20 was associated with a 5.5% DCS isopleth after 6 hours.

A few cases had DCS symptoms on arrival to P2 and were assigned a failure time of 1 minute. Symptoms and VGE in a few subjects developed during depress from 10.2 psia to 4.3 psia in studies where 10.2 psia was a staged depressurization step without prior prebreathe before depressurization from 14.7 psia to 10.2 psia 12 hours earlier. Clearly, "silent bubbles" had formed at 10.2 psia within tissues that later manifested in symptoms during depress from 10.2 psia to 4.3 psia. Some small risk of DCS (about 3%) and larger risk of VGE (about 40%) is estimated for the 10.2 psia (see Table 2) exposure but no symptoms were reported at 10.2 psia nor were subjects monitored for VGE at 10.2 psia. A few cases had the first report of a symptom after the test, during the medical debriefing, and were assigned failure times as the censored times.

Our survival models predicted more DCS and VGE than anticipated (see Table 2 entries for 10.2 psia tests) given a 15-minute depressurization to 10.2 psia without prior prebreathe, even when followed by 12 hours or more at 10.2 psia breathing 26.5% O_2 before 3 to 6 hours at 4.3 psia. We should have monitored for VGE during the many hours at 10.2 psia because a few subjects had VGE detected during the first monitoring interval at 4.3 psia. In other words, depress to 10.2 psia even after 60 minutes of prebreathe and a slow depress of 25 minutes resulted in VGE in a few subjects. Additional evidence to support this conclusion is as follows: A brief 30-minute exposure to 10.2 psia followed by a repressurization to 14.7 psia before a final depress to 4.3 psia was significant to reduce the subsequent risk of DCS and VGE – possibly because a subset of large "silent bubbles" started to grow at 10.2 psia but were later eliminated during the intervening 100 minutes at 14.7 psia. This condition was significant enough to include as an explanatory variable (see REP designation in 8th column of Table 2) in our 3 regression models. The application of a pressure spike before depressurization is shown in animal models to reduce the risk of subsequent DCS (Vann *et al*. 1980, Butler *et al*. 2006).

Our regression models have not been rigorously validated in prospective testing or other validation techniques, so in the strictest sense we have only described our data. Our approach is to update regressions as additional data become available. Caution is warranted when our regressions are used to predict novel depressurizations, as done for the EA.

6.0 CONCLUSIONS

Equation 1 was described and accounts for denitrogenation in any prebreathe of arbitrary complexity. Rules were documented on how to account for exercise as part of the prebreathe protocol. The ratio of final $P_{tis}N_2$ to P2 at the start of the hypobaric exposure defines the decompression dose as TR. TR and other explanatory variables were combined along with survival and censored times in log-logistic survival models to then estimate the P(DCS $T < t$), P(VGE $T < t$), and P(Grade IV VGE $T < t$) for promising new protocols. It was discussed with P2s other than 4.3 psia that an alternative survival model (Conkin *et al*. 1996b) be used to estimate P(DCS $T < t$). The TBDM was briefly described and BGI as an alternative index of decompression dose was evaluated in the same set of data. The goodness-of-fit of the BGI-based regressions was less than for TR-based regressions. However, the BGI-based regressions are a better option to the TR-based regressions when P2 is not 4.3 psia.

APPENDIX A

Examples of Applying Equation 1

Equation 1 (or Eq. 3 in this case) is used to calculate the final $P_{tis}N_2$ and then a decompression dose as TR at the start of the low-pressure exposure. Two examples are provided:

1. A 60-minute resting 100% O_2 prebreathe at 14.7 psia is followed by a 15-minute depressurization to 6.0 psia.

$P_{a,i-1}$ = 11.61 psia (14.7 psia × 0.79% N_2)
P_{ai} = 0 (100% O_2 has no PN_2)
Δt_i = 75 minutes (resting, no exercise planned for the prebreathe)
$k_i = \frac{e^{\lambda \dot{V}_{O_2} i}}{519.37}$ = $e^{(0.03 \times 0)}$ / 519.37 = 0.001925, 360.0 $t_{1/2i}$ (Rule 2)
s_i = 0 (no average rate of change of PN_2 because 100% O_2 has no PN_2, which reduces Eq. 1 to Eq. 3).
$P_{tis}N_2(i) = 10.04$ psia
TR = $P_{tis}N_2(i)$/P2 = 10.049/6.0 = 1.675

From regressions described earlier, the P(DCS) after the resting prebreathe for a 4-hour exposure to 6.0 psia with BMI = 24, AMB = 1, and REP = 0 is 20.2% (16.5 – 24.5%, 95% CI), the P(VGE) after the resting prebreathe for a 4-hour exposure to 6.0 psia with AGE = 32, SEX = 1, AMB = 1, and REP = 0 is 58.8% (53.8 – 63.6%, 95% CI), and for the same inputs used in P(VGE) the P(Grade IV VGE) is 33.5% (28.6 – 38.9%, 95% CI).

2) A 60-minute 100% O_2 exercise prebreathe at 14.7 psia with 2 10-minute intervals of exercise at 23.5 mL $O_2 \times kg^{-1} \times min^{-1}$ starting at T = 0 and T = 40 mins with intervals of rest between the exercise is then followed by a resting 15-minute depressurization with 50% O_2 – 50% N_2 to 6.0 psia.

Example 1 had one 75-minute interval while example 2 has 7 in the same 75 minutes.

$P_{a,i-1}$ = 11.61 psia (14.7 psia × 0.79% N_2)
P_{ai} = 0 (100% O_2 has no PN_2)
Δt_i = 10-minute (exercise 1)
$k_i = \frac{e^{\lambda \dot{V}_{O_2} i}}{519.37}$ = $e^{(0.03 \times 23.5)}$ / 519.37 = 0.00389, 178.2 $t_{1/2i}$ (Rule 3,4)
s_i = 0 (no average rate of change of PN_2 because 100% O_2 has no PN_2)
$P_{tis}N_2(i) = 11.167$ psia
==========
$P_{a,i-1}$ = 11.167 psia
P_{ai} = 0 (100% O_2 has no PN_2)
Δt_i = 5-minute (transition 1)
transitional O_2 consumption rate = 23.5 – 3.5 / 2 = 10.0 mL $O_2 \times kg^{-1} \times min^{-1}$ (Rule 3)

$k_i = \frac{e^{\lambda \dot{V}_{O_2} i}}{519.37}$ = $e^{(0.03 \times 10.0)}$ / 519.37 = 0.003508, 266.7 $t_{1/2i}$ (Rule 3)
s_i = 0 (no average rate of change of PN_2 because 100% O_2 has no PN_2)
$P_{tis}N_2(i) = 11.023$ psia
==========
$P_{a,i-1}$ = 11.023 psia
P_{ai} = 0 (100% O_2 has no PN_2)
Δt_i = 25-minute (resting 1 after exercise)
$k_i = \frac{e^{\lambda \dot{V}_{O_2} i}}{519.37}$ = $e^{(0.03 \times 3.5)}$ / 519.37 = 0.00213, 325.4 $t_{1/2i}$ (Rule 3)
s_i = 0 (no average rate of change of PN_2 because 100% O_2 has no PN_2)
$P_{tis}N_2(i) = 10.451$ psia
==========
$P_{a,i-1}$ = 10.451 psia
P_{ai} = 0 (100% O_2 has no PN_2)
Δt_i = 10-minute (exercise 2)
$k_i = \frac{e^{\lambda \dot{V}_{O_2} i}}{519.37}$ = $e^{(0.03 \times 23.5)}$ / 519.37 = 0.00389, 178.2 $t_{1/2i}$ (Rule 3,4)
s_i = 0 (no average rate of change of PN_2 because 100% O_2 has no PN_2)
$P_{tis}N_2(i) = 10.053$ psia
==========
$P_{a,i-1}$ = 10.053 psia
P_{ai} = 0 (100% O_2 has no PN_2)
Δt_i = 5-minute (transition 2)
transitional O_2 consumption rate = 23.5 – 3.5 / 2 = 10.0 mL $O_2 \times kg^{-1} \times min^{-1}$ (Rule 3)
$k_i = \frac{e^{\lambda \dot{V}_{O_2} i}}{519.37}$ = $e^{(0.03 \times 10.0)}$ / 519.37 = 0.00260, 266.7 $t_{1/2i}$ 8 (Rule 3)
s_i = 0 (no average rate of change of PN_2 because 100% O_2 has no PN_2)
$P_{tis}N_2(i) = 9.923$ psia
==========
$P_{a,i-1}$ = 9.923 psia
P_{ai} = 0 (100% O_2 has no PN_2)
Δt_i = 5 min (resting 2 after exercise)
$k_i = \frac{e^{\lambda \dot{V}_{O_2} i}}{519.37}$ = $e^{(0.03 \times 3.5)}$ / 519.37 = 0.00213, 325.4 $t_{1/2i}$ (Rule 3)
s_i = 0 (no average rate of change of PN_2 because 100% O_2 has no PN_2)
$P_{tis}N_2(i) = 9.818$ psia
==========
$P_{a,i-1}$ = 9.818 psia
P_{ai} = 7.35 (50% O_2 and 50% N_2 at 14.7 psia has 7.35 psia PN_2)
Δt_i = 15-minute (resting 3 during depress after exercise)
$k_i = \frac{e^{\lambda \dot{V}_{O_2} i}}{519.37}$ = $e^{(0.03 \times 3.5)}$ / 519.37 = 0.00213, 325.4 $t_{1/2i}$ (Rule 3)
s_i = 0.29 psia PN_2 / min (7.35 psia PN_2 @ 14.7 psia – 3.0 psia PN_2 @ 6.0 psia) / 15 min)
$P_{tis}N_2(i) = 9.671$ psia
TR = $P_{tis}N_2(i)$/P2 = 9.671/6.0 = 1.612

From regressions described earlier, the P(DCS $T < t$) after the exercise prebreathe for a 4-hour exposure to 6.0 psia with BMI = 24, AMB = 1, and REP = 0 is 15.0% (12.0 to 18.3%, 95% CI), the P(VGE $T < t$) after the exercise prebreathe for a 4-hour exposure to 6.0 psia with AGE = 32, SEX = 1, AMB = 1, and REP = 0 is 52.8% (47.9 to 57.6%), and for the same inputs used in P(VGE $T < t$) the P(Grade IV VGE $T < t$) is 27.8% (23.3 to 32.8%).

APPENDIX B

Bubble Growth Index as Decompression Dose

Tissue ratio ($P_{tis}N_2$/P2) as decompression dose takes into account the prebreathe conditions and the final test exposure pressure. Tissue ratio defines the "general" whole-body decompression stress at the start of the exposure, and then variables such as the exposure duration, the type and intensity of exercise during the exposure, and physical characteristics of the subjects contribute to the final DCS and VGE outcomes. TR is an abstraction of the true decompression dose and more details about TR are available (Conkin *et al*. 1998a). Other expressions of decompression dose can be evaluated, such as Bubble Growth Index (BGI) from the Tissue Bubble Dynamics Model (TBDM). The BGI is the ratio of final (largest) bubble radius during the exposure to an initial 3 micron micronuclei radius (see Gernhardt 1991 and Conkin *et al*. 2014 for more details). The decompression dose is a spherical bubble growing in a 1 cm^3 of tissue with a 360-minute half-time to account for nitrogen kinetics. The BGI is more constrained than TR as an index of decompression dose; it is specific while TR is general. If 1 bubble growing in a theoretical tissue with 360-minute half-time kinetics is linked to the report of a symptom or the presence of VGE in the pulmonary artery, then BGI would be an ideal expression of decompression dose. The BGI has been used as the basis of several logistic regression models at JSC (Abercromby *et al.* 2015). Both TR and BGI as decompression dose account for the prebreathe conditions and the final test exposure pressure. But other constants are associated with bubble growth and resolution and were established as part of the TBDM before use in our laboratory.

We provide in Appendix B the summary regression results for BGI as the decompression dose. In all cases, the goodness-of-fit of the predicted versus the observed DCS, VGE, and Grade IV VGE is greater for TR than for BGI given that all other conditions are identical. From a practical perspective, TR can be computed by hand with the aid of a calculator, even if a bit tedious when exercise is part of the prebreathe (Eq. 1). Computing BGI by hand is not possible; it requires access to the TBDM computer program. However, there are complex situations where P2 varies over short intervals of time or when P2 is > 5.0 psia, which limits the application of TR (see Discussion on Limitations and Applications). The BGI and a probabilistic logistic regression model (Abercromby *et al.* 2015) or survival models (described below) can be applied even though the goodness of fit of BGI in our data is less than for TR. Perhaps expressing BGI as a bubble volume index and referencing the numerator and denominator volumes at body temperature, pressure, and saturated with water vapor (BTPS) would result in a better hypobaric decompression dose than TR (Van Liew & Burkard 1995).

Table 1B lists the 49 tests, details of each test (e.g., P2, TR, BGI, duration, demographics), the observed incidence of DCS, VGE, and Grade IV VGE for each test. Additional information for each row is located in Table 2. There were 577 subjects (431 men and 146 women) that participated in 49 tests covering 1,031 hypobaric exposures (834 exposures with men and 192 exposures with women). Abbreviations for column headings are provided in the Methods.

Table 1B. Summary of NASA DCS, VGE, and Grade IV VGE Results with Mean BGI

Test	P2 (psia)	Duration (hr)	Sample m	f	Mean age	DCS cases	DCS (%)	Mean TR	Mean BGI	VGE (any Grade)	VGE (Grade IV)
1a	4.3	3	11	0	34.5	4	36.3	1.75	29.7	7	4
1b	4.3	3	13	0	32.3	3	23.0	1.81	56.3	11	7
1b10.2	10.2	12	13	0	32.3	0	0	1.13	19.7	n/a	n/a
1c	4.3	3	12	0	32.0	4	33.3	1.64	53.7	7	6
1c10.2	10.2	12	12	0	32.0	0	0	1.13	19.7	n/a	n/a
1d	4.3	3	3	0	39.6	2	66.6	1.70	58.6	3	2
1d10.2	10.2	18	3	0	39.6	0	0	1.13	21.9	n/a	n/a
2a	4.3	4	23	0	31.6	7	30.4	1.69	35.7	15	8
2b	4.3	4	22	0	31.5	6†	27.3	1.74	64.7	10	7
2b10.2	10.2	12	22	0	31.5	0	0	1.13	19.5	n/a	n/a
3a	4.3	6	28	0	31.0	6	21.4	1.60	41.9	13	11
3b	4.3	6	35	0	30.1	8	22.8	1.67	45.2	20	8
3b10.2	10.2	12	35	0	30.1	0	0	1.01	1.0	n/a	n/a
3c	4.3	6	14	0	32.5	3	21.4	1.35	29.7	5	1
3d	4.3	6	12	0	28.5	2	16.6	1.40	32.5	5	2
4a	4.3	3	12	0	30.1	1	8.3	1.67	28.0	7	3
4a10.2	10.2	12	12	0	30.1	0	0	1.01	1.0	n/a	n/a
4b	4.3	3	12	0	30.1	0	0	1.10	36.4	2	1
4c	4.3	3	12	0	30.1	0	0	1.36	18.7	4	1
4d	4.3	3	12	0	30.1	0	0	0.94	19.0	0	0
4e	4.3	3	12	0	30.1	0	0	1.34	18.0	4	1
4f	4.3	3	12	0	30.1	0	0	0.92	17.7	0	0
5a	4.3	6	19	19	31.5	4	10.5	1.31	28.5	11	4
5b	4.3	6	11	0	32.0	0	0	1.04	1.0	0	0
6	6.0	6	15	14	32.9	1	3.4	1.22	21.1	3	0
610.2	10.2	24	15	14	32.9	0	0	0.89	1.0	n/a	n/a
7a	6.5	3	11	0	28.2	4††	36.3	1.78	25.6	8	6
7b	6.5	3	11	0	28.2	2	18.2	1.78	25.6	8	4
8a	6.5	3	29	11	32.4	7	17.5	1.78	25.6	20	13
8b	6.5	3	30	11	32.6	10†	24.4	1.78	25.5	22	17
9a	6.5	3	15	9	32.1	1	4.1	1.78	25.6	12	7
9b	6.5	3	14	9	33.8	2†	8.7	1.78	25.6	6	1
9c	4.3	3	9	2	34.8	3	27.3	1.66	25.6	5	4
9d	4.3	3	6	1	36.4	0	0	1.66	24.7	2	0
9e	4.3	3	7	0	34.5	0	0	1.46	21.4*	2	0
10	10.11	3	14	5	31.7	1	5.2	1.22	17.0	6	3
11a	4.3	4	16	12	33.2	3	10.7	1.85	38.5	9	4
11b	6.5	2	1	3	39.5	0	0	1.75	18.2	1	0
P I	4.3	4	35	14	29.4	9	18.3	1.87	41.7*	24	2
P II	4.3	4	38	12	32.2	0	0	1.85	40.8*	15	3

P III	4.3	4	8	2	29.4	2†	20.0	1.92	43.4*	2	1
P IV	4.3	4	50	15	30.4	8	12.3	1.90	42.8*	26	9
V-1	4.3	4	7	3	31.2	3	30.0	1.99	43.9*	6	2
V-2	4.3	4	2	2	42.0	1†	25.0	2.02	42.7*	4	2
V-3	4.3	4	39	11	36.9	7	14.0	1.86	41.3*	25	5
V-4	4.3	4	4	3	31.1	3	42.8	1.75	35.8*	3	1
V-5	4.3	4	38	11	32.1	2	4.1	1.73	36.3*	14	8
Nuc-1	4.3	4	16	5	36.4	4	20.0#	1.85	40.8*	13	6
Nuc-3	4.3	4	32	9	36.0	2	4.8	1.85	40.9*	11	4

P2 is the ambient pressure in the hypobaric chamber, n/a is not applicable because monitoring for VGE was not performed, † 1 case was classified as Type II DCS, †† 2 were classified as Type II DCS. *prebreathe included prescribed exercise, all others were resting during prebreathe. # 1 case of left ventricular gas emboli in Nuc-1 was removed early so total count for %DCS = 20.

Table 2b summarizes regression results for DCS, VGE, and Grade IV VGE that include BGI. The 5th column shows the *P*-values given that all explanatory variables (Full Model) were evaluated in the regression. We rejected an explanatory variable if the *P*-value was > 0.05. The 4th column shows the *P*-values for the final explanatory variables used in the regression (Nested Model). $\beta_{(1)}$ (scale) and $\beta_{(2)}$ (location) are fitted parameters specific to the log-logistic survival model, SE is standard error of the parameter estimate. A negative sign on the estimate indicates a greater probability of the event for a larger value of the explanatory variable.

Two goodness-of-fit statistics: Akaike Information Criterion (AIC) and Schwarz's Bayesian Information Criterion (BIC), were computed for regressions that included BGI and compared to earlier regressions with TR. The results are included in the legends of Figs. 1B, 2B, and 3B. In summary, the 3 TR-based models have 1 more explanatory variable than the BGI-based models and yet the 3 models have lower AIC and BIC values than the 3 models with BGI as decompression dose. TR as decompression dose reduces the difference between observed and predicted DCS, VGE, and Grade IV VGE outcomes more so than BGI as decompression dose.

Table 2B. Log-Logistic Survival Results with BGI as Decompression Dose

DCS 125 in 1,031	Nested Model			Full Model
Parameter	Estimate	SE	*P*-value	*P*-value
$\beta_{(1)}$	0.926	0.0747	<0.001	<0.001
$\beta_{(2)}$	6.469	0.595	<0.001	<0.001
AGE	-0.022	0.0112	0.041	0.042
SEX	-	-	-	0.297
BMI	-	-	-	0.206
BGI	-0.059	0.007	<0.001	<0.001
AMB	-0.498	0.200	0.012	0.342
REP	-	-	-	0.074

AIC = 1,092.6
Schwarz's BIC = 1,117.3

VGE 368 in 903	Nested Model			Full Model
Parameter	Estimate	SE	*P*-value	*P*-value
$\beta_{(1)}$	1.0219	0.047	<0.001	<0.001
$\beta_{(2)}$	4.612	0.425	<0.001	<0.001
AGE	-0.0345	0.0083	<0.001	<0.001
SEX	-0.437	0.1809	0.015	0.01
BMI	-	-	-	0.37
BGI	-0.033	0.0067	<0.001	<0.001
AMB	-0.558	0.144	<0.001	0.044
REP	-	-	-	0.084

AIC = 2,965.6
Schwarz's BIC = 2,991.4

GIV VGE 166 in 903	Nested Model			Full Model
Parameter	Estimate	SE	*P*-value	*P*-value
$\beta_{(1)}$	0.940	0.0667	<0.001	<0.001
$\beta_{(2)}$	6.499	0.617	<0.001	<0.001
AGE	-0.0508	0.0103	<0.001	<0.001
SEX	-0.5174	0.251	0.038	0.139
BMI	-	-	-	0.30
BGI	-0.0266	0.0074	<0.001	<0.001
AMB	-1.125	0.2016	<0.001	<0.001
REP	-	-	-	0.287

AIC = 1,648.3
Schwarz's BIC = 1,676.0

Akaike Information Criterion: AIC = -2log-likelihood + 2k, where k is the number of parameters estimated. Model selection using AIC is based on the principle of parsimony. The idea of model selection using AIC is to select a model with a low AIC value.

Schwarz provided a Bayesian Information Criterion for model selection: Schwarz's BIC = -2log-likelihood + $k \times \log(n)$, and again the idea is to select a model with a low BIC value.

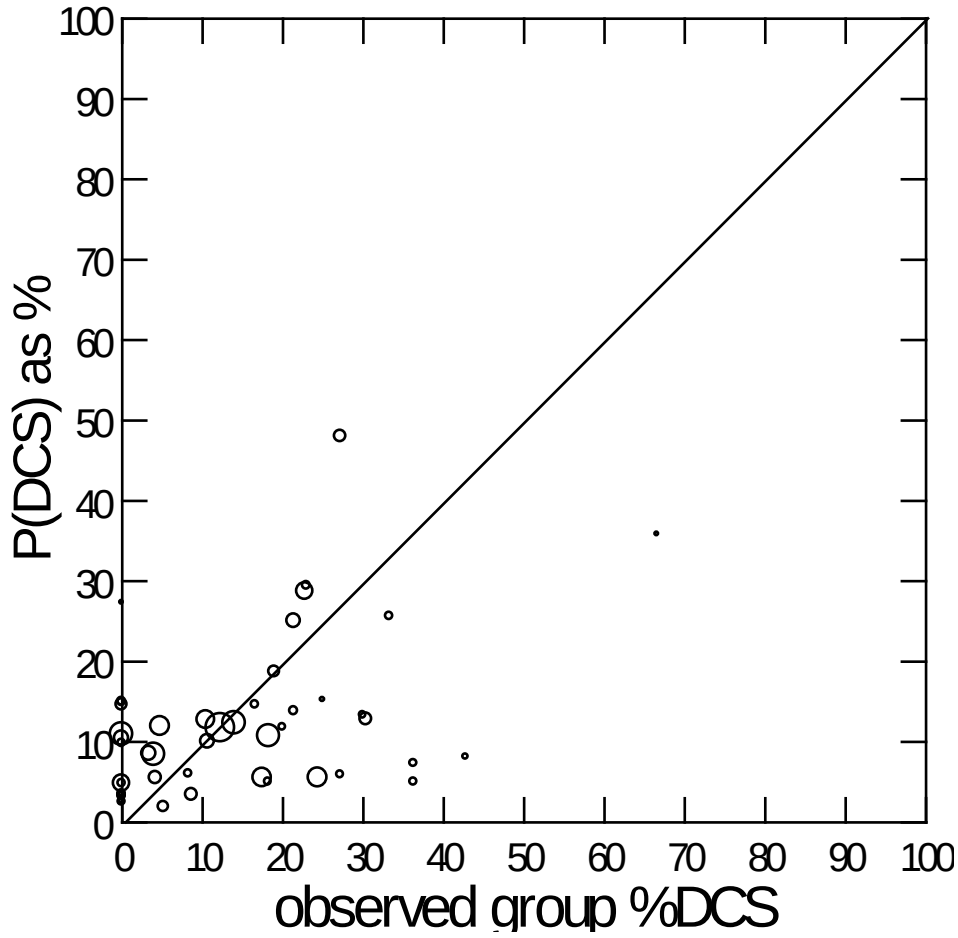

Fig. 1B. Observed versus predicted DCS based on 125 cases in 1,031 exposures from 49 tests using 577 subjects. Area of circles reflects sample size from 49 tests, smallest group size was 3 and largest was 65. Goodness of fit summary statistics AIC = 1,092.6 and Schwarz's BIC = 1,117.3 to compare with TR-based DCS regression AIC = 1,024.6 and Schwarz's BIC = 1,054.2.

$$P(DCS\ T< t) = 1 / (1+\exp(-(\ln(t) - 6.469 + 0.059\times BGI + 0.498\times AMB + 0.022\times AGE) / 0.926)),$$

where P(DCS $T < t$) is the probability that survival time T for DCS is $< t$, that DCS will be observed in the interval between 0 and t ($0 \leq T < t$), t is in hours from start of exposure at the test pressure (P2), bubble growth index (BGI) is the ratio of final bubble radius to initial 3 micron micronucleus radius, ambulation status (AMB) is either 1 or 0, which indicates that ambulation is part of the physical activity in the hypobaric chamber, and AGE is subject age in years.

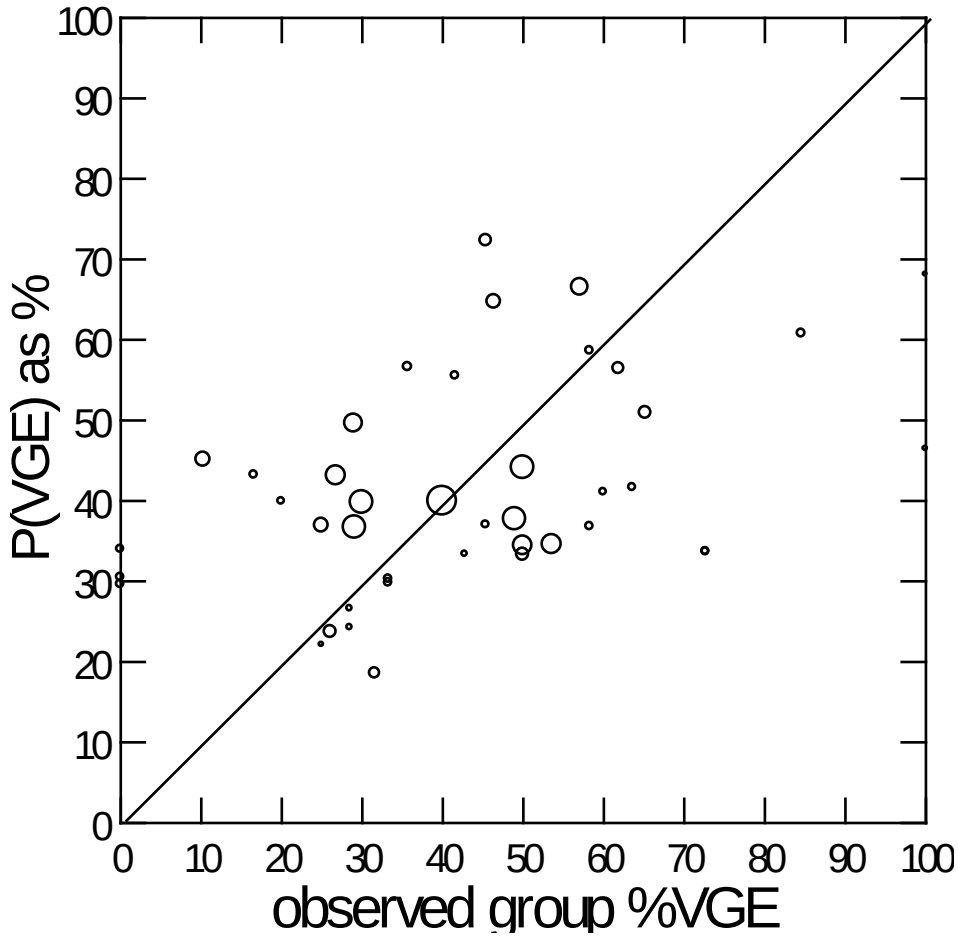

Fig. 2B. Observed versus predicted VGE based on 368 cases in 903 exposures from 42 tests using 577 subjects; 7 tests were long exposures ≥ 12 hours to 10.2 psia as part of a staged denitrogenation protocol and no VGE monitoring was performed. Area of circles reflects sample size from 42 tests, smallest group size was 3 and largest was 65. Goodness of fit summary statistics AIC = 2,965.6 and Schwarz's BIC = 2,991.4 to compare with TR-based VGE regression AIC = 2,881.0 and Schwarz's BIC = 2,911.2.

$$P(\text{VGE } T < t) = 1 / (1+\exp(-(\ln(t) - 4.612 + 0.0345\times\text{AGE} + 0.033\times\text{BGI} + 0.437\times\text{SEX} + 0.558\times\text{AMB}) / 1.021))$$

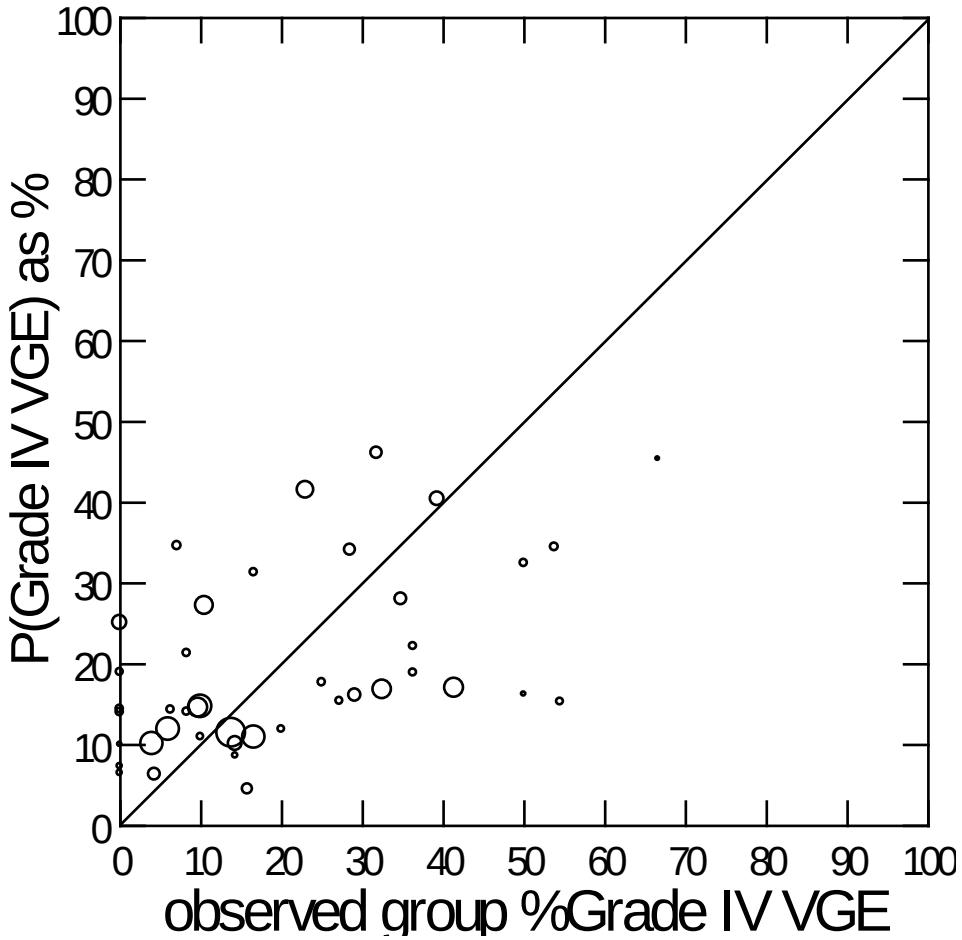

Fig. 3B. Observed versus predicted Grade IV VGE based on 166 cases in 903 exposures from 42 tests using 577 subjects; 7 tests were long exposures ≥ 12 hours to 10.2 psia as part of a staged denitrogenation protocol and no VGE monitoring was performed. Area of circles reflects sample size from 42 tests, smallest group size was 3 and largest was 65. Goodness of fit summary statistics AIC = 1,648.3 and Schwarz's BIC = 1,676.0 to compare with TR-based Grade IV VGE regression AIC = 1,592.7 and Schwarz's BIC = 1,624.9.

$$P(\text{Grade IV VGE } T < t) = 1 / (1+\exp(-(\ln(t) - 6.499 + 0.0508\times\text{AGE} + 0.0266\times\text{BGI} + 0.517\times\text{SEX} + 1.125\times\text{AMB}) / 0.94))$$

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REFERENCES

Abercromby AFJ, Conkin J, Gernhardt ML. Modeling a 15-min extravehicular activity prebreathe protocol using NASA's exploration atmosphere (56.5 kPa / 34% O_2). *Acta Astronautica* 2015; 109:76-87.

Chadov VI, Iseyev LR. Variations in the maximal allowable supersaturation coefficient during altitude decompression. *Kosm Biol Aviak Med* 1989; 23:58-62. [English abstract in: Hooke LR, Teeter R, Donaldson PL, ed. USSR space life science digest. NASA CR-3922(28), Issue 24, Springfield, VA: National technical Information Service, 1989: 94-5].

Butler BD, Little T, Cogan V, Powell MR. Hyperbaric oxygenation pre-breathe modifies the outcome of decompression sickness. *Undersea Hyperb Med* 2006; 33:407-17.

Conkin J. Probabilistic Modeling of Hypobaric Decompression Sickness. Doctoral Dissertation. State University of New York at Buffalo, 1994.

Conkin J. A log-logistic survival model applied to hypobaric decompression sickness. In: Weathersby PK, Gerth WA (ed.). *Survival Analysis and Maximum Likelihood Techniques as Applied to Physiological Modeling*. 51st Workshop of the Undersea and Hyperbaric Medical Society, Seattle, WA, 19 May, 1998, Kensington, MD: Undersea and Hyperbaric Medical Society; 75-93.

Conkin J. Evidence-based approach to the analysis of serious decompression sickness with application to EVA astronauts. Houston, TX: NASA Johnson Space Center; January 2001. NASA Technical Publication 2001-210196.

Conkin J, Abercromby AFJ, Dervay JP, Feiveson AH, Gernhardt ML, Norcross JR, Ploutz-Snyder R, Wessel JH, III. Hypobaric decompression sickness treatment model. *Aerosp Med Hum Perform* 2015; 86:508-17.

Conkin J, Abercromby AFJ, Dervay JP, Feiveson AH, Gernhardt ML, Norcross J, Ploutz-Snyder R, Wessel JH, III. Probabilistic assessment of treatment success for hypobaric decompression sickness. Houston, TX: NASA Johnson Space Center; November 2014. NASA Technical Publication NASA/TP-2014-218561.

Conkin J, Foster PP, Powell MR, Waligora JM. Relationship of the time course of venous gas bubbles to altitude decompression illness. *Undersea Hyperbaric Med* 1996a; 23:141-49.

Conkin J, Foster PP, Powell MR. Evolved gas, pain, the power law, and probability of hypobaric decompression sickness. *Aviat Space Environ Med* 1998a; 69:352-9.

Conkin J, Gernhardt ML, Abercromby AFJ, Feiveson AH. Probability of hypobaric decompression sickness including extreme exposures. *Aviat Space Environ Med* 2013; 84:661-8.

Conkin J, Gernhardt ML, Powell MR, Pollock NW. A probability model of decompression sickness at 4.3 psia after exercise prebreathe. Houston, TX: NASA Johnson Space Center; December 2004. NASA Technical Publication 2004-213158.

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

Conkin J, Pollock NW, Natoli MJ, Martina SD, Wessel JH, III, Gernhardt ML. Venous gas emboli and ambulation at 4.3 psia. *Aerosp Med Hum Perform* 2017; 88:370-76.

Conkin J, Powell MR. Lower body adynamia as a factor to reduce the risk of hypobaric decompression sickness. *Aviat Space Environ Med* 2001; 72:202-14.

Conkin J, Powell MR, Foster PP, Waligora JM. Information about venous gas emboli improves prediction of hypobaric decompression sickness. *Aviat Space Environ Med* 1998b; 69:8-16.

Cox DR, Oakes D. Analysis of Survival Data. New York, NY: Chapman and Hall; 1984:13-21.

Gernhardt ML. Development and Evaluation of a Decompression Stress Index Based on Tissue Bubble Dynamics [dissertation]. Philadelphia, PA: University of Pennsylvania; 1991.

Lee ET. Statistical Methods for Survival Data Analysis, 2nd ed. New York, NY: John Wiley and Sons; 1992:8-18 and 191-93.

Spencer MP (1976). Decompression limits for compressed air determined by ultrasonically detected blood bubbles. *J Appl Physiol* 40(2): 229-35.

Steinberg D, Preston D, Clarkson D, Colla P. Survival analysis: supplementary module for SYSTAT 13 (Chap. 12). In: *SYSTAT13:* Statistics IV, Chicago, IL: SYSTAT Software, Inc.; 2009: IV-401-68.

Thompson LA, Conkin J, Chhikara RS, Powell MR. Modeling Grade IV venous gas emboli using a limited failure population model with random effects. NASA Technical Publication 2002-210781, Houston: Johnson Space Center, June 2002.

Van Liew HD, Burkard ME. Simulation of gas bubbles in hypobaric decompressions: roles of O_2, CO_2, and H_2O. *Aviat Space Environ Med* 1995; 66:50-5.

Vann RD, Grimstad J, Nielsen CH. Evidence for gas nuclei in decompressed rats. *Undersea Biomed Res* 1980; 7:107-12.

Webb JT, Krock LP, Gernhardt ML. Oxygen consumption at altitude as a risk factor for altitude decompression sickness. *Aviat Space Environ Med* 2010; 81:987-92.