A PROBABILITY MODEL OF DECOMPRESSION SICKNESS AT 4.3 PSIA AFTER EXERCISE PREBREATHE

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Acronyms and Nomenclature

BMI	Body Mass Index
CEV	Crew Excursion Vehicle
DCS	Decompression Sickness
EVA	Extravehicular Activity
ETR	Exercise Tissue Ratio
H_2O	water
ISS	International Space Station
JSC	Johnson Space Center
LR	Logistic Regression
LL	log likelihood
NASA	National Aeronautics and Space Administration
NM	NASA Model
N_2	nitrogen
O_2	oxygen
pk	peak
PRP	Prebreathe Reduction Protocol
psia	pounds per square inch absolute
PB	prebreathe
ppN_2	partial pressure of nitrogen
ppO_2	partial pressure of oxygen
RM	Research Model
SD	standard deviation
TR	Tissue Ratio
VGE	Venous Gas Emboli

Abstract

Exercise during oxygen (O_2) prebreathe (PB) accelerates nitrogen (N_2) removal from the tissues. Exercise PB can reduce the risk of decompression sickness (DCS) on ascent to 4.3 psia when performed at the proper intensity and duration. We hypothesized that a probability model with a variable half-time compartment to compute the decrease in tissue N_2 pressure given specifics about exercise during the PB would be superior to a model based on a constant 360 min half-time compartment. Data are from seven tests. PB times ranged from 90 to 150 min. High intensity, short duration dual-cycle ergometry was done during the PB for seven min at 75% of peak O_2 consumption after a three min warm-up period at the start of PB. This was done by itself, or in combination with intermittent low intensity exercise or periods of rest for the remaining PB. Variations of exercise intensity in later tests reflected exercise that could be performed in a space suit. PBs in 167 exposures also included a 30-min exposure to 10.2 psia where subjects breathed 26.5% O_2 − 73.5% N_2, and all tests used a 30 min ascent to 4.3 psia. Non-ambulating men and women performed light exercise from a semi-recumbent position at 4.3 psia for four hrs. DCS at 4.3 psia was reported during 28 exposures, with two classified as Type II DCS. The exercise intervals for each subject was defined as the percentage of VO_2 pk with unit $mL*kg^{-1}*min^{-1}$ while rest intervals were assigned 9.5% of VO_2 pk. Some otherwise useful data did not have a measure of VO_2 pk. To exploit all the available data, we developed a Research Model (n = 229) with estimated VO_2 pk for 65 subjects, and a NASA Model (n = 159), all with measured VO_2 pk. An iterative approach established the best relationship between %VO_2 pk for each exercise and rest interval and the half-time for N_2 removal or uptake. The best-fit logistic model using decompression dose defined as computed tissue N_2 pressure at the end of ascent divided by ambient pressure (always 4.3 psia) was obtained with a nonlinear relationship between half-time and percentage of VO_2 pk. With this approach, aerobic fitness should relate to DCS outcome if aerobic fitness did indeed relate to DCS outcome, regardless if the exercise during the PB was characterized as relative work, absolute work, or a combination of both. The Research Model with age included improved over the null model by 7.5 log likelihood units, and over a model with a constant 360 min half-time compartment by 4.0 units. Both improvements were statistically significant. The probability of DCS increases with advancing age. The NASA Model with gender included improved over the null model by 7.7 log likelihood units, and over a model with a constant 360 min half-time compartment by 4.1 units. Both improvements were statistically significant. The probability of DCS increases if gender is female. Accounting for exercise and rest during PB with a variable half-time compartment for computed tissue N_2 pressure advances our probability modeling of hypobaric DCS. Both models show that a small increase in exercise intensity during PB expressed as a percentage of VO_2 pk reduces the risk of DCS, and a larger increase in exercise intensity dramatically reduces risk. These models support the hypothesis that aerobic fitness is an important consideration for the risk of hypobaric DCS when exercise is performed during the PB.

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Introduction

Fundamental Cause of Decompression Sickness:

Equation 1 defines a fundamental axiom about decompression sickness (DCS), which is that a transient gas supersaturation, known as pressure difference (ΔP), exists in a tissue region. The sum of all gas partial pressures in that region is greater than the ambient pressure opposing the release of the gas. Supersaturation exists when ΔP is positive:

$$\Delta P = \sum_{i=1}^{k} P_1 - P2, \qquad \text{Eq. 1}$$

where P_1 is the partial pressure of the ith gas of k species in the tissue and P2 is the ambient pressure after depressurization. The potential for bubble growth and rate of bubble growth are related to the magnitude of the supersaturation. The metabolic gases: oxygen (O_2), carbon dioxide (CO_2), and even water vapor (H_2O) at 37 c are controlled by physiology within narrow limits, so under most circumstances the inert gas partial pressure is the critical concern. Although gas supersaturation in the tissue is not in itself harmful, it is nevertheless an un-stable condition between the tissue and the surrounding environment. The difference in tissue gas partial pressure and ambient pressure can be resolved with a phase transition, and some of the excess mass (moles) of gas in the form of bubbles would be accommodated by the tissue, causing no symptoms. However, when a gas space is formed due to the partial or complete desaturation of a supersaturated tissue, there is a possibility of DCS. The determining factor of DCS may not be the presence or even absolute volume of evolved gas in the tissue, but rather the pressure difference (deformation pressure) between the gas space and the tissue.

Prevention of Decompression Sickness with Oxygen Prebreathe:

For aviators and astronauts the nitrogen (N_2) partial pressure (ppN_2) in the tissues is a concern. A 75 kg man at sea level pressure (one atmosphere absolute [ATA]) with 15% of total body weight as fat carries about one liter of N_2 dissolved in the tissues and fluids. About half (500 ml at standard temperature and pressure [STP]) is contained in 63 kg of "lean" tissues and body fluids and about half is contained in 12 kg of "lipid" tissues. During a 4-hr 100% O_2 resting prebreathe (PB) about 750 ml STP is removed, leaving only 250 ml STP in the tissues. However, an ascent to 1/3 ATA has the potential of transforming the 250 ml into 750 ml of evolved gas (simple application of Boyles Law). This worst-case scenario is never realized because the formation of bubbles takes time, time which is also available for additional N_2 removal from the tissues via the lungs, and not all supersaturation results in bubble formation.

Exercise as a Means to Accelerate Nitrogen Washout:

Prebreathing O_2 while at rest is the simplest and most widely used risk mitigation strategy to prevent altitude DCS (26,34). Exercise during PB increases the rate of N_2 removal and shortens the PB time (3,4,6,55,57,58). This technique is successful because blood perfusion through tissues is the rate limiting process for N_2 washout during the PB, and exercise increases tissue blood perfusion in metabolically active tissues (34,53).

Two approaches are used to quantify the benefit of exercise during PB: measuring the N_2 removed during the PB (see Fig. 1), and measuring the decrease in incidence of DCS and venous gas emboli (VGE) during subsequent exposure to reduced pressure (54). The latter is the approach we have used (8,20,21,22,24). But there are many unanswered questions about using exercise to accelerate N_2 washout and thus shorten the PB time. What is the best exercise to use in terms of the type, intensity, and duration for maximum effect? Besides fatigue and dehydration, what are the contraindications for exercise during PB? Any kinetic motion in the body has the potential of forming micronuclei through tribonucleation (27,31), either stabilized or transient micronuclei. Micronuclei act as "seeds" to facilitate the transformation of dissolved gas into evolved gas (bubbles) during subsequent exposure to reduced pressure (18,29,50,52).

So there is a complex balance between the goal of accelerating N_2 washout with exercise and the potential to form micronuclei that could grow into bubbles on subsequent depressurization.
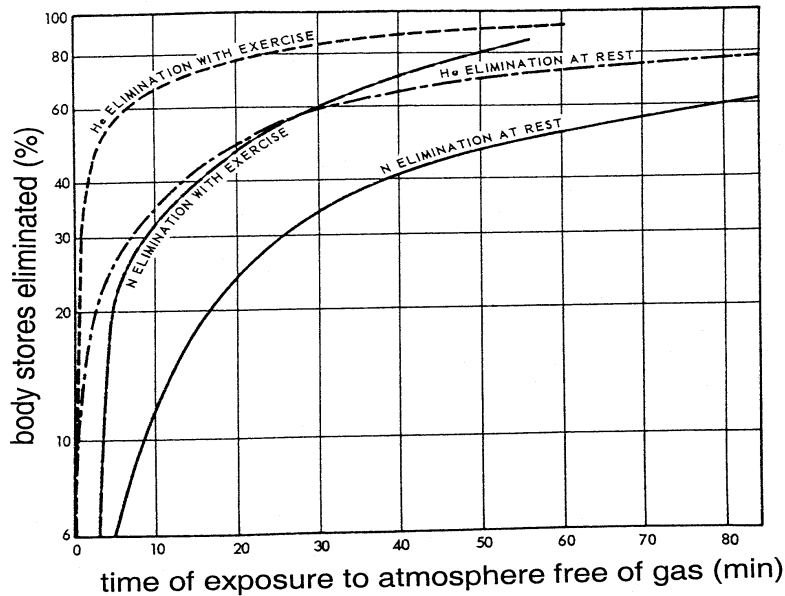
Figure 1. A greater amount of N_2 and He are removed if exercise is used during PB (5).

Purpose of Report:

This report documents one analytical approach to quantify the benefit of exercise during PB to reduce the risk of DCS in subjects exposed to 4.3 psia. We quantify the risk by estimating the probability of DCS [P(DCS)] given the conditions of the PB and altitude exposure. Our analysis extends the work of others (37,39,41). Data are describe from seven tests that define the NASA Prebreathe Reduction Protocol (PRP) initiated in 1999, and a statistical analysis of those data is performed. Two models are developed: the first is called the NASA Model (NM), based on 159 exposures specific to the needs of NASA, and the second is called the Research Model (RM), based on 229 exposures specific to address other research questions.

Exercise During Prebreathe:

Both the shuttle and International Space Station (ISS) operate at 14.7 pounds per square inch absolute (psia) with an air atmosphere, so a PB procedure is required to reduce N_2 partial pressure in the tissues to an acceptable level prior to depressurization to 4.3 psia. Exercise during PB is an effective way to reduce tissue ppN_2 and therefore the risk of DCS during a subsequent EVA. However, the magnitude of the benefit given specifics about the exercise type, intensity, and duration needs to be quantified.

It is known that exercise before a decompression in divers (63,17) and aviators (16), during decompression in divers (32,33), during O_2 PB (3,4,6,54,55,57), and certainly during the altitude exposure (1,14,30,35) influences the DCS or VGE outcomes. Exercise is a powerful stimulus to the body, so it is reasonable to expect that the type, intensity, duration, and timing of exercise before a depressurization would modify the outcome (also see Adynamia Section).

It is known that older men are at greater risk of DCS than younger men (9,10,25,28,49). Overweight men are at a greater risk of DCS than underweight men (1,15,25). Therefore, overweight older men are expected to be at a greater risk of DCS than underweight younger men. But how do you interpret the case of an underweight older man or overweight younger man? What is needed is an explanatory variable that is better associated with the decompression outcome than just age or body type. It is also desirable that the explanatory variable has some rational causal relationship to the development of DCS, not just a correlative relationship.

The removal of N_2 from the tissues during a denitrogenation procedure is limited by blood perfusion (34,53). Therefore, a fit person will eliminate more N_2 than an unfit person during an exercise-enhanced O_2 PB with the exercise intensity prescribed as a percentage of maximum O_2 consumption. Aerobic fitness declines with advancing age regardless of our individual efforts.   Declines of 0.7% and 1.6% are reported for elite male athletes in categories of most active to least active, respectively, as they age from 25 to 40 years (38). Concomitant decreases in aerobic fitness and not the increase in age *per se* may be responsible for a greater risk of DCS (9,40,43). Similarly, overweight people generally have lower aerobic fitness that continues to decrease as they become more obese. Some women are less fit than men, which may give credence to the still controversial observations that females are at greater risk of DCS

than males (13,36,45,46,56,64). The relationship between aerobic fitness and age, body type, and gender may help to explain why some fit older men are less likely to contract DCS than some unfit younger men. Therefore we used aerobic fitness defined as maximum O_2 consumption (VO_2 max) with unit mLO_2 consumption $(STPD)*kg^{-1}*min^{-1}$ as one important explanatory variable for DCS, especially under conditions when N_2 is removed from the body during exercise PB. Age, body type, and even gender are potentially confounding correlative explanatory variables. In effect, they are poor surrogates for aerobic fitness to understand the risk of DCS after a denitrogenation procedure.

We will show that a probability model for DCS based on the *hypothesis* that DCS risk after exercise PB based on a percentage of VO_2 pk is inversely related to aerobic fitness. We will show that this is better than other alternatives we evaluate.

Relative and Absolute Exercise (work) During Prebreathe:

There is a peculiarity in how this model is structured to account for relative and absolute work during an exercise PB that needs to be clearly stated. The model is fundamentally based on the hypothesis that aerobic fitness affects DCS outcome when the PB includes exercise to accelerate N_2 washout. We believe that subjects with high VO_2 pk are less likely to contract DCS after exercise PB compared to subjects with low VO_2 pk that perform the same exercise PB regardless of the type of exercise performed. Since high intensity, short duration exercise in our testing was assigned at 75%, 60%, 50%, etc., of VO_2 pk, the fit subject would actually consume more O_2 than the unfit subject. However, all exercise during PB in our testing was not prescribed as a percentage of VO_2 pk. We also assigned low intensity, long duration absolute work using various "crank-and-yank" devices mounted on an exercise cot. When a constant amount of work is prescribed, a fit or unfit person will still do the same total work. This means, baring any difference in exercise efficiency, a similar O_2 consumption for performing absolute work is expected, whether one is fit or unfit.

A limitation of our analysis is that there were no measurements of O_2 consumption in subjects during the exercise PB as they performed relative work as defined by a percentage of VO_2 pk using dual-cycle ergometers, absolute work on the crank-and-yank devices, or a combination of both in the same PB protocol. Instead, a measure of VO_2 pk was the only information available for most subjects. The O_2 consumption as $ml*kg^{-1}*min^{-1}$ for relative work based on a percentage of VO_2 pk was computed for the appropriate interval of time when this type of exercise was done. So the fit and unfit subjects were assigned the appropriate O_2 consumption for the exercise interval. This same approach was extended to assign O_2 consumption for exercise intervals where crank-and-yank absolute work was done. This is not strictly correct since absolute work would demand the same O_2 consumption whether the person is fit or unfit. But in our statistical model there are two practical advantages of taking this approach: you at least reference the estimate of O_2 consumption to a measurement of VO_2 pk that is available for the subject that actually performed the PB, and you preserve in the model the idea that fitness is related to DCS outcome when PB procedures use exercise to accelerate N_2 washout regardless of the type of exercise. To account for exercise during PB given both relative and absolute work with one methodology, we impose that a fit person will consume slightly more O_2 than an unfit person given that both perform low intensity, long duration absolute work.

The parameter estimates in the statistical models developed here maximize correlative relationships between explanatory variables and the response variable regardless if the model is based on a sound theoretical rationale. If a fit person does low intensity, long duration absolute work and does not contract DCS and the unfit person does the same work and contracts DCS, then the model will reflect this result by making small changes in O_2 consumption as $ml*kg^{-1}*min^{-1}$ important. If fitness during absolute work is not an important consideration, then the model will not be influenced by small changed in O_2 consumption using our methodology. An alternative is to assign a constant (mean) O_2 consumption in the interval for the crank-and-yank absolute work to each subject who performed that exercise. The assigned mean O_2 consumption would not be related to the only information collected for the subject, the VO_2 pk. The constant

would come from a representative sample of subjects. This alternative approach results in losing the opportunity to test for the importance of fitness given low intensity absolute work since the model is not provided with a distinction between fit or unfit subjects.

By what rationale do we favor a statistical model based on classifying both absolute and relative work as a percentage of VO_2 pk? Figure 2 is based on an initial analysis before the Results section to make this crucial point. If VO_2 pk for the subject correlates to the DCS outcome, even if the exercise during the PB was based on absolute or relative work, then a methodology that preserves this correlation should be used.
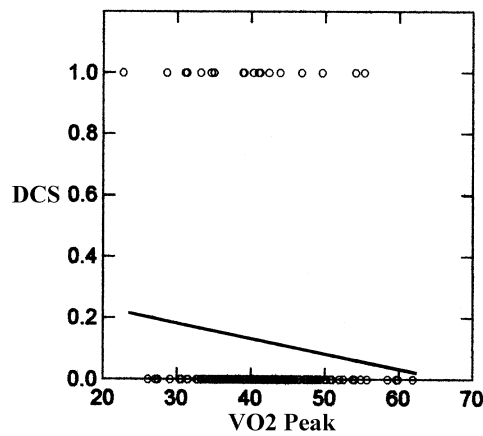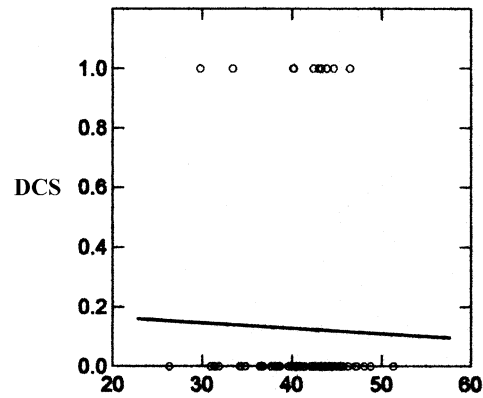
Figure 2. The correlation trend between DCS outcome and VO_2 pk from exposures where absolute work was done during the PB (upper panel) and when a combination of absolute work and relative work was done (lower panel).

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The upper panel in Fig. 2 shows a modest inverse trend between DCS outcome and VO_2 pk in 71 exposures from Phases III and IV in data used in the RM. Note that VO_2 pk in 64 of these exposures had to be estimated from other information about the test subjects (explained later). These data are for exercises during PB classified as absolute work. The mean VO_2 pk in 10 subjects with DCS is 40.73 ± 5.2 mL$*$kg$^{-1}*$min^{-1} and 41.01 ± 4.7 in 61 subjects without DCS. Contrast this to a greater inverse trend (steeper slope) in the lower panel between DCS outcome and VO_2 pk in 152 exposures from Phases I, II, V-1, V-2, and V-3 in data used in the NM. These data are for exercise during PB just classified as relative work (percentage of VO_2 pk in Phase I) plus data where both relative exercise and absolute exercise were both done during the PB (Phases II, V-1, V-2, and V-3). The mean VO_2 pk in 20 subjects with DCS is 38.95 ± 8.4 mL$*$kg$^{-1}*$min^{-1} and 41.78 ± 7.3 in 132 subjects without DCS. Unfortunately, we do not have enough data to evaluate the case where just relative work (only in Phase I) was done during the PB. A tentative conclusion is that aerobic fitness is inversely associated with DCS outcome whether only absolute work is performed during the PB (upper panel) and certainly if a combination of relative and absolute work is performed (lower panel).

We maximize the above correlative information about VO_2 pk and DCS outcome in a statistical model even if it conflicts with exercise physiology theory about O_2 consumption during absolute work. But how would you use this correlative information? One approach is to preserve the linkage to VO_2 pk for each subject by referencing all exercise to VO_2 pk, which takes advantage of one methodology. A second approach is to provide mean O_2 consumption for absolute work without the link to VO_2 pk, and then include VO_2 pk as a covariate in all future models to capture its contribution in a disjointed data file. A third approach is to actually measure O_2 consumption for both types of exercise during the PB on the day of the test in each subject that goes to altitude. We currently exploit the first approach. The second approach is possible, but more complicated than the first since the data about exercise is disjointed, containing one methodology for relative work and one methodology for absolute work. The second approach requires that you deal with covariate interactions since you essentially use VO_2 pk information twice, once to characterize relative work and once as a stand-alone covariate to

address any correlation with DCS outcome and absolute work. This requires additional degrees of freedom in the model, which may not be statistically justified compared to a simpler approach. The third option is the best approach, but is not how we have conducted this research.

In summary, tissue metabolic needs dictate the distribution of cardiac output. The distribution of cardiac output during a PB dictates the quality of the denitrogenation from the tissues. The limited blood volume cannot be distributed equally into the total volume of the capillary beds; there is exquisite physiological regulation of blood perfusion. When the exercise during PB is developed around relative work (a percentage of VO_2 pk), then a fit person will consume more O_2 than an unfit person, and more O_2 consumption indicates increased perfusion, and therefore greater N_2 washout. The fit person will have a lower decompression stress at the end of the PB, as reckoned by a lower Exercise Tissue Ratio (ETR), to be defined later. When the exercise during PB is a set amount of work, both fit and unfit persons will achieve about the same O_2 consumption, and each will have the same decompression stress. Our statistical approach is to use one methodology throughout the varied exercise performed during the PB to estimate the O_2 consumption based on a percentage of VO_2 pk.

Methods

Data: Exercise and Prebreathe

All subjects signed Informed Consent, were trained on the breathing and exercise equipment in the altitude chamber, received special training on the recognition and reporting of DCS, and were free to withdrawal at any time during the test. Three laboratories used altitude chambers to perform research over a four-year period: Duke University, Defense Research and Development Canada at Toronto, and the University of Texas in conjunction with Hermann Hospital. The respective Institutional Review Boards reviewed and approved all protocols prior to testing.

Seven tests are available for analysis. There were four tests, designated Phase I, II, III, and IV, where subjects performed exercise during the PB, ascended to 10.2 psia and breathed

26.5% O_2 for 30 min, then completed a 40 min PB on 100% O_2. Three tests, designated as Phase V-1, V-2, and V-3, also included exercise during the PB, but there was no PB at 10.2 psia. All seven tests included a 30 min ascent from 14.7 psia and exposure to 4.3 psia for four hrs. All subjects performed regimented crank-and-yank exercise at 4.3 psia to simulate EVA activities. Subjects were adynamic (non-ambulatory) for two hrs before the start of the PB, during the PB, and while at 4.3 psia for four hrs. Total PB time ranged from 120 to 180 min. Total PB time included the 30 min to ascend to 4.3 psia and the 30 min at 10.2 psia in Phases I – IV where the subjects breathed 26.5% O_2 through a mask.

The PB and ascent profile for the seven tests were complex in that various exercises during PB were performed, and the ascent to 4.3 psia in Phases I - IV was staged at 10.2 psia for 30 min. After 50 min of PB at site pressure, the subjects in Phases I – IV ascended to 9.6 psia in 20 min followed by a 10-min descent to 10.2 psia, still breathing 100% O_2. The gas supply was switched in the mask, and the subjects then breathed 73.5% N_2 and 26.5% O_2 for 30 min while at 10.2 psia. One hundred percent O_2 PB was reestablished and a five min descent to site pressure was performed. The subjects remained on 100% O_2 for 35 min at site pressure and during the final 30-min ascent to 4.3 psia. An Appendix provides details too numerous to summarize here about the seven tests.

Adynamia:

Adynamia is defined as the absence of ambulation, even a standing posture, during both the PB phase at site pressure and during the exercise phase while at altitude. This is currently our best analogue for μ-gravity adaptation (11,42). Subjects exercised the lower body while at altitude and were still classified as adynamic since they did not ambulate during the PB or while at altitude. This means that an adynamic person at altitude exercised from a semi-recumbent position, and we do not know how this exercise modified the adynamic condition. The results from these tests were used to define safe and effective PB procedures for astronauts performing EVAs from the ISS.

The fundamental untested premise of adynamia is about the control of nucleation processes within tissues and fluids (16,42,59). A comprehensive review of micronuclei is beyond the scope of this report. In the absence of supersaturation, as defined in Eq. 1, the spontaneous rate of nucleation is inconsequential when micronuclei on the order of microns in radius are considered. This is not to say, however, that the number or distribution of micronuclei sizes cannot be influenced before a supersaturation exists when mechanical energy is added to the system. A case in point is the observation that vigorous exercise during a 90 min PB reduces, not increases, the incidence of DCS and VGE (55). The enhanced removal of N_2 during the dual-cycle exercise appears to dominate the DCS and VGE outcomes, regardless of how the number or distribution of micronuclei were changed. Since the tests have low decompression stress by design, it is important to control all variables that can modify the outcome. When ambulation is controlled through forced adynamia, then other variables such as age or gender that may correlate to DCS or VGE outcome can be better understood. Our control of adynamia is also the reason that the probability models in this report are specific to astronauts that perform EVAs.

Table 1 summarizes the explanatory (independent) variables for data used in the RM, and Table 2 is the summary for data used in the NM.

TABLE 1. Summary Statistics for RM Explanatory Variables

Explanatory Variables	n	mean	SD	range
1. AGE (yrs)	229	31.9	8.3	18 – 59
2. WT (kg)	229	77.3	13.8	46 – 118
3. HT (cm)	229	176.7	8.7	148 – 198
4. BMI (kg/m^2) Body Mass Index	229	24.6	3.2	17 – 35
5. VO_2 pk* ($mL*kg^{-1}*min^{-1}$)	229	41.47	6.8	22.7 – 62.1
6. TPBTM (min)** Total Prebreathe Time	229	171	18	120 – 197

7. GENDER	175 male
	54 female
8. Exercise #1	49
9. Exercise #2	47
10. Exercise #3	9
11. Exercise #4	62
12. Exercise #5	9
13. Exercise #6	3
14. Exercise #7	50

* contains both measured (n=164) and estimated (n=65) VO_2 pk.

** includes 30 min ascent to 4.3 psia in all tests and 30 min at 10.2 psia in Phases I - IV

TABLE 2. Summary Statistics for NM Explanatory Variables

Explanatory Variables	n	mean	SD	range
1. AGE (yrs)	159	32.8	8.6	19 – 59
2. WT (kg)	159	77.7	14.3	46 – 115
3. HT (cm)	159	176.7	8.9	148 – 198
4. BMI (kg/m^2) Body Mass Index	159	24.7	3.4	17 – 35
5. VO_2 pk ($mL*kg^{-1}*min^{-1}$)	159	41.39	7.4	22.7 – 61.9
6. TPBTM (min)* Total Prebreathe Time	159	166	19	120 – 180
7. GENDER	120 male 39 female			
8. Exercise #1	47			
9. Exercise #2	45			
10. Exercise #3	4			
11. Exercise #4	3			

12. Exercise #5	9
13. Exercise #6	3
14. Exercise #7	48

* includes 30 min ascent to 4.3 psia in all tests and 30 min at 10.2 psia in Phases I - IV

The first six variables are measured on a continuous scale, and the last eight are indicator variables taking only the values of zero or one. Even though there is a wide range for each continuous variable, the relatively small standard deviation (SD) for each variable indicates a homogeneous sample. This homogeneity is due to pretest medical selection criteria and a desire to match the physical characteristics of current U.S. astronauts. We do not separate the variables by gender, so this does contribute to a larger sample SD in height and weight in the combined data.

Exercise During Prebreathe:

The last seven variables in Tables 1 and 2 identify the type and duration of exercise done during the PB. Some details about the specific exercise during the PBs are covered now, with more details provided in the Appendix. Exercise #1 is 10 min of dual-cycle arm and leg ergometery initiated at the start of PB, and performed at 75% of pk O_2 consumption for the last seven min. No additional exercise was allowed for the balance of the 150 min O_2 PB. Exercise #2 is the same exercise as Exercise #1 plus 24 min of additional intermittent light arm and leg exercise starting 55 min into the PB and ending 95 min after the start of PB. Here, heavy short-duration ergometry exercise was coupled with light intermittent short-duration exercise during the later part of the PB. Exercise #3 is the same 24 min of intermittent light arm and leg exercise also starting 55 min into the PB and ending 95 min after the start of PB. There was one case of Type II DCS in this protocol, and the testing was ended. Exercise #4 is 56 min of intermittent light long-duration arm and leg exercise that started four min into the PB and ended 95 min from the start of the PB. Exercise #5 is ten 2-min exercise and rest cycles with exercise between 40 – 60% of VO_2 pk in the first 44 min of PB followed by 46 min of rest. Exercise #6 is seven 3-min exercise and 2-min rest cycles with exercise between 50 – 60% of VO_2 pk in the first 44 min of PB followed by 46 min of rest. There was one case of Type II DCS in this protocol, and the

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testing was ended. Finally, Exercise #7 is seven 3-min exercise and 2-min rest cycles with exercise between 50 – 60% of VO_2 pk in the first 36 min of PB followed by 24 min of light activity in 54 min followed by 30 min of rest.

In a typical logistic regression (LR), the contribution of the different exercise options during the PB to the DCS outcome would have to be coded, and six estimated parameters would be produced. An example of the coding of the PB conditions that could be used in a regression for the data in Table 1 is as follows: a one indicates the presence of Exercise #1 in 47 exposures and zero for the balance of 182 exposures, and so on for the six remaining exercise PB categories. This approach is not desirable here (is not parsimonious), and is replaced with a method that accounts for exercise during PB by a trial-and-error optimization of a single parameter called λ.

Assigning %VO_2 pk O_2 Consumption for Intervals of Relative Work:

Figure 3 is helpful in describing our method to assign normalized O_2 consumption $(mL*kg^{-1}*min^{-1})$ during intervals of relative and absolute work during the PB. Exercise intervals of relative work using dual-cycle ergometry were assigned O_2 consumption normalized to body weight by taking a percentage of VO_2 pk.
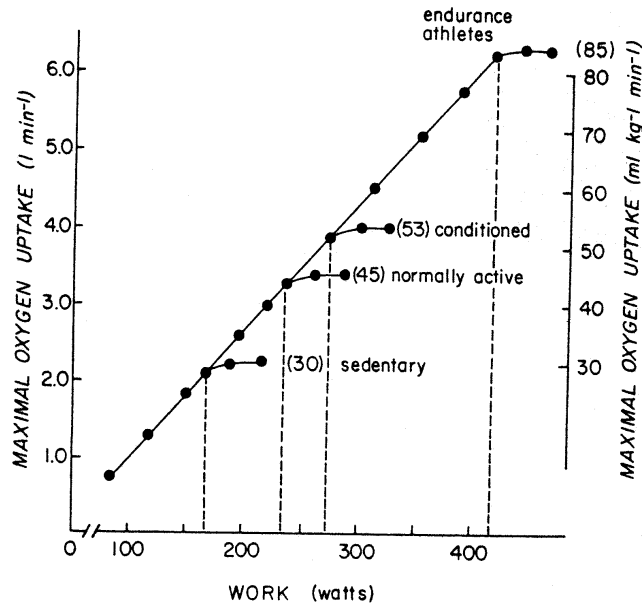
Figure 3. Linear relationship between O_2 uptake and workload up to the VO_2 max. Thereafter, O_2 uptake reaches a plateau as work rate increases (44).

Under idea conditions, the subject increases work load (watts) with a technique that does not fatigue a particular muscle group until the time the subject decides to stop the exercise after a maximum effort, a time that provides for an accurate measure of VO_2 maximum. In our testing, dual-cycle ergometry was used on a schedule described in the Appendix. We prefer to use the terminology VO_2 pk since our methodology was not standard. Dual-cycle ergometry was also used during the PB and an exercise prescription based on percentage of VO_2 pk was assigned, for example, 75%, 60%, 50% VO_2 pk. In this way, each subject performed the same exercise relative to his or her VO_2 pk. The absolute O_2 consumption using this approach is always greater for the fit subject compared to the unfit subject. A benefit of this approach is that the aerobic fitness of the subject is linked to O_2 consumption during an interval of time since the exercise is referenced to the VO_2 pk of the subject.

Assigning %VO_2 pk O_2 Consumption for Intervals of Absolute Work:

There were also intervals during the PB when absolute work was assigned. The exercise cot was equipped with various devices that required the subject to crank-and-yank, using bungee cord and a torque wrench as described in the Appendix. If each subject was equally motivated, and all advantages of having long limbs can be ignored, then we assume that all subjects performed the same absolute work. Figure 3 shows that each subject would be assigned a constant O_2 consumption based on the amount of absolute work, irrespective of the aerobic fitness of the subject. A sample of 17 subjects representative of those that performed the test at 4.3 psia performed these crank-and-yank exercises and O_2 consumption was measured. The mean and SD were 5.8 ± 0.7 mL$*$kg$^{-1}*$min^{-1}. The mean VO_2 pk in a sample of five women and nine men was 42.2 ± 6.0 mL$*$kg$^{-1}*$min^{-1}, with a mean age of 35 years. One approach would be to assign a constant 5.8 mL$*$kg$^{-1}*$min^{-1} to each interval of work in each subject that actually went to 4.3 psia that performed this absolute work during the PB. However, this approach eliminates the only linkage to information about the fitness of the subject that actually went to 4.3 psia, the VO_2 pk for the subject. For reasons explained in more detail later, we chose to reference this absolute work to the VO_2 pk of the subject to preserve a linkage to VO_2 pk in our statistical treatment of these data. Exercise intervals of absolute work using crank-and-yank devices mounted on the exercise cot were also assigned O_2 consumption normalized to body weight by taking a percentage of VO_2 pk. The absolute work was converted to 13.8% of VO_2 pk by dividing mean 5.8 mL$*$kg$^{-1}*$min^{-1} by mean 42 mL$*$kg$^{-1}*$min^{-1} from our sample of subjects that did not go to 4.3 psia. In this way, one methodology was used to link all O_2 consumption to the fitness of the subject in our statistical approach even though this is contrary to our understanding about exercise physiology under conditions of absolute work. This approach was also extended to characterize intervals of rest. True resting (basal) conditions were not achieved in subjects anxious about the test and never told to truly rest, and 9.5% of VO_2 pk was assigned based on a measure under similar conditions of 4.0 ± 0.5 mL$*$kg$^{-1}*$min^{-1} in our sample of 17 subjects. Therefore, none of the exercise in our seven tests was characterized as only relative work since all tests included intervals of rest during the PB. The closest was Phase I. All had both types of exercise, absolute and relative, characterized based on a percentage of VO_2 pk. We justify using a percentage of VO_2 pk for intervals of absolute work from our

sample of subjects to subjects that actually went to 4.3 psia because the mean VO_2 pk in these subjects was about 42 mL$*$kg$^{-1}*$min^{-1}. Subjects used in both the RM and NM had mean VO_2 pk of 41.5 ± 7.5 mL$*$kg$^{-1}*$min^{-1}.

Table 3 shows the type of exercise activity in the intervals that define the total exercise during the PB in Phases I through V-3, the assigned percentage of VO_2 pk, and the time of the interval. All of these intervals were defined as a percentage of VO_2 pk for the subject that went to altitude. The early tests included simpler exercise profiles compared to later tests as evident by fewer intervals of defined exercise activity. The characterization of VO_2 pk for relative work in the Phase V series (V-1, V-2, and V-3) was also less accurate since a confirmed steady state exercise condition was not achieved due to short intervals of relative exercise, two min in V-1 and three min in V-2 and V-3. The targets for the Phase V series were 40%, 50%, and 60% VO_2 pk. The actual performance from a representative sample of subjects that never went to altitude was 32%, 38%, and 45% in V-1 since subjects never reach a steady state with the 2-min exercise. In the construction of the exercise PB protocol for the Phase V series, 30%, 36%, and 45% of VO_2 pk was used in V-1, and is considered representative of what was actually done on the day of the test. Since exercise at 60% VO_2 pk in V-2 and V-3 went for three min, 60% VO_2 pk was assigned for the last two min of the exercise. The estimate of the exercise PB just needed to approximate the representative measured values. Exact measured data from each subject that went to 4.3 psia would be ideal, but we do not have these data. Finally, the slow 30 min ascent from 14.7 to 4.3 psia is part of each exercise PB, and we assigned 9.5% VO_2 pk to this last part of the PB.

TABLE 3: Intervals that Define the Exercise Done During Prebreathing

Phase	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
I	W	R	T	T	Q	Q	Q									
% VO_2	37.5	75.0	37.5	25.0	9.5	9.5	9.5									
time	3	7	3	17	50	30	70									
II	W	R	T	T	Q	A	A	Q	Q							
% VO_2	37.5	75.0	37.5	25.0	9.5	13.8	13.8	9.5	9.5							
	3	7	3	17	35	15	15	15	70							

time																
III	Q	A	A	Q	Q											
%VO$_2$	9.5	13.8	13.8	9.5	9.5											
time	65	15	15	15	70											
IV	Q	A	A	Q	Q											
%VO$_2$	9.5	13.8	13.8	9.5	9.5											
time	4	76	15	15	70											
V-1	Q	R	R	T	R	R	T	R	R	T	R	R	T	R	R	T
%VO$_2$	9.5	30.0	30.0	25.0	36.0	36.0	25.0	45.0	45.0	25.0	45.0	45.0	25.0	45.0	45.0	25.0
time	2	1	1	2	1	1	2	1	1	2	1	1	2	1	1	6
V-2	R	R	T	W	R	T	T	W	R	T	T	W	R	T	T	W
%VO$_2$	36.0	36.0	25.0	30.0	60.0	30.0	25.0	30.0	60.0	30.0	25.0	30.0	60.0	30.0	25.0	30.0
time	1	1	2	1	2	1	1	1	2	1	1	1	2	1	3	1
V-3	Q	R	T	W	R	T	T	W	R	T	T	W	R	T	T	W
%VO$_2$	9.5	36.0	25.0	30.0	60.0	30.0	25.0	30.0	60.0	30.0	25.0	30.0	60.0	30.0	25.0	25.0
time	2	2	2	1	2	1	1	1	2	1	1	1	2	1	3	1

TABLE 3: Continuation of V-1, V-2, and V-3

Phase	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32
V-1	R	R	T	R	R	T	R	R	T	R	R	T	R	R	T	Q
%VO2	45.0	45.0	25.0	45.0	45.0	25.0	45.0	45.0	25.0	45.0	45.0	25.0	39.0	39.0	25.0	9.5
time	1	1	2	1	1	2	1	1	2	1	1	2	1	1	10	66
V-2	R	T	T	W	R	T	T	W	R	T	Q	Q				
%VO2	60.0	30.0	25.0	30.0	60.0	30.0	25.0	30.0	60.0	30.0	9.5	9.5				
time	2	1	1	1	2	1	1	1	2	1	10	75				
V-3	R	T	T	W	R	T	T	W	R	T	Q	A	Q	Q		
%VO2	60.0	30.0	25.0	30.0	60.0	30.0	25.0	30.0	60.0	30.0	9.5	13.8	9.5	9.5		
time	2	1	1	1	2	1	1	1	2	1	13	40	30	30		

R = relative work (dual-cycle ergometry)
A = absolute work (crank-and-yank devices)
Q = quiet (rest) periods
T = transition from high intensity, low duration exercise to low intensity, long duration exercise, or transition from relative work to rest
W = warm up work (ramping up to dual-cycle relative work)

There was also a desire to account for total O_2 consumption in these tests by adjusting the percentage of VO$_2$ pk in a few intervals, mostly in the intervals designated as transition from high intensity, low duration exercise to low intensity, long duration exercise, or transition from relative work to rest. This was done so that the computed total O_2 consumption would reflect the measured O_2 consumption from a sample of subjects from Duke University and JSC that performed the exercise PB but never went to altitude. The transition from one exercise condition to another is expected to be a source of variability in O_2 consumption. The rationale was that since little is know about the O_2 consumption during the transition from exercise in the actual subjects that went to altitude, it would be reasonable to adjust the percentage of VO$_2$ pk in that interval such that computed total O_2 consumption would be similar to measured O_2 consumption from a sample of subjects.

Table 4 shows a comparison of estimated cumulative O_2 consumption in exposures used in the RM, which includes O_2 consumed during the time at 10.2 psia in Phases I through IV and during the 30-min ascent in all tests, to what was measured in a sample of 19 subjects for Phases I - IV, and 18 subjects for Phase V-1. There were no measurements available for V-2 and V-3.

TABLE 4: Estimated versus Measured O_2 Consumption During Exercise Prebreathe

Phase	estimated O_2 consumption (liters, STPD)	n	measured O_2 consumption (liters, STPD)	n
I	76.5 ± 20.1	49	73.1 ± 14.3	19
II	88.1 ± 20.7	47	79.1 ± 15.6	19
III	60.2 ± 6.2	9	58.5 ± 9.4	19
IV	66.7 ± 12.3	62	65.5 ± 11.9	19
V-1	78.4 ± 15.5	9	75.0 ± 12.6	18
V-2	62.0 ± 28.5	3	no baseline data collected	

| V-3 | 92.5 $\pm$ 22.2 | 21 | no baseline data collected |

===

We conclude that the relative ranking of O_2 consumption is preserved, that the absolute values of the estimated O_2 consumption are similar to a sample of measured values, and that our adjustments of O_2 consumption as subjects transitioned from relative work to rest or other absolute work is reasonable.

Exercise at 4.3 psia:

Intermittent upper and lower body exercise began for all subjects on reaching 4.3 psia for four hrs. The exercise continued until the end of the test or until the subject was removed from the chamber, mostly due to DCS. The subjects performed three bouts of repetitive four-min exercises under adynamic conditions while in a semi-recumbent position. There was a four-min period for bubble monitoring, and also a four-min period of rest after every 60 min. The subjects were encouraged to report any symptoms, and the attending physician made a diagnosis of DCS if warranted. Most of those with a diagnosed symptom of DCS were immediately removed from the altitude chamber through a transfer lock. Termination criteria did not permit subjects to remain at altitude with any persistent symptom(s). As a result, some of the VGE data is right censored, which means the test was ended earlier than planned. The details of the exercise during the PB and during the time at 4.3 psia are documented in the Appendix.

Doppler Ultrasound Bubble Monitoring:

A Doppler Technician using a transcutaneous Doppler ultrasound bubble detector monitored the blood flow in the pulmonary artery, central venous blood, for bubbles. The VGE monitoring was performed approximately every 12 min for four min. While in a semi-recumbent position, the subject was prompted to flex each of his limbs in turn three times to dislodge VGE from the tissue capillaries and improve VGE detection and grading. Trained observers used the audio signal from the bubble detector to assign a grade for VGE from each of the four limbs on the zero to four Spencer scale (47). This report is about quantifying the risk of DCS, so we limit

an extensive description of methodology and the resulting information about VGE to just a few summary statements and three figures at the end of the Results. The Grade of VGE is mentioned, so we paraphrase the definitions as originally published by Spencer: Grade 0 is the complete lack of bubble signals in all cardiac cycles, Grade I is the occasional bubble signal detected in a cardiac cycle with the majority of cardiac cycles free of bubble signals, Grade II is when many, but less than half, of the cardiac cycles contain bubble signals, Grade III is when most of the cardiac cycles contain bubble signals, but not overriding the cardiac motion signals, and Grade IV is 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.

VO$_2$ Pk Measured or Estimated:

There are 229 records acceptable for analysis in the RM given that 65 records are provided an estimate of VO$_2$ pk. Except for the absence of measured VO$_2$ pk, these 65 records are valuable and should not be omitted if possible. Since it is reasonable to assume that VO$_2$ pk (aerobic fitness) is related to age, weight, and certainly gender, we constructed a multivariable linear regression model to estimate VO$_2$ pk for males and females given their age, weight, and height. There were 86 records for males and 30 records for females with measured VO$_2$ pk available when the regressions were performed. All the details about the regressions are not provided. Equation 2 is for males and Equation 3 is for females, and were applied to the height, weight, and age data for the 65 records (50 males and 15 females) that did not have a measured VO$_2$ pk.

VO$_2$ pk (♂) = 24.274–0.175(age)–0.122(wt)+0.64(ht), n = 86   Eq. 2

VO$_2$ pk (♀) = 49.481+0.027(age)–0.184(wt)+0.15(ht), n = 30   Eq. 3

This manipulation did not over or under represent these 65 records in that the mean VO$_2$ pk was 40.9 mL$*$kg$^{-1}*$min^{-1} $\pm$ 4.6 SD compared to 41.7 mL$*$kg$^{-1}*$min^{-1} $\pm$ 7.5 SD for the balance of 164 records in the RM where VO$_2$ pk was actually measured. There are 159 records acceptable for analysis in the NM, with a mean VO$_2$ pk of 41.4 $\pm$ 7.4 SD. The smaller set of data for the NM is mainly due to the exclusion of those 65 records without a measured VO$_2$ pk.

In this way, two models are evaluated that exploit all the available data and exploit the best available data.

Selection of Data for RM and NM:

Table 5 documents the rationale to include or exclude data from the NM and the RM. The data for the NM could be characterized as all those data that were acceptable to test the primary hypothesis about accepting or rejecting the PB protocol being evaluated. For example, if the total PB time exceeded five min then the result of the test could not be used to test the hypothesis about the PB procedure, and therefore would not qualify to be included in the NM. However, the exercise PB model does account for the PB conditions, so tests that went long on PB time still qualify to be included in the RM. Other specifics are contained in Table 5.

TABLE 5: Selection of Specific Model Data

NASA Model	Research Model	PRP Phase
no cases were included where PBs were longer than specified for the test since results were used to accept or reject the PB procedure	13 cases where PBs were extended are included since the model accounts for PB time	2 in Phase I 3 in Phase II 8 in Phase IV
3 cases classified as ambiguous DCS outcome that did not stop the test early are included as cases of no DCS	none of 5 cases classified as ambiguous DCS outcome were included: 2 cases stopped the test early and 3 cases did not stop the test early	1 in Phase II 2 in Phase IV 1 in Phase IV that stopped early 1 in Phase V-1 that stopped early
2 cases that reported symptoms after the test are included	no cases that report symptoms after the test are included	2 in Phase I
2 cases were stopped early due to DT with DCS, and not included	2 cases were stopped early due to DT with DCS, and not included	2 in Phase II
2 cases classified as Type II are included with others classified as Type I	2 cases classified as Type II are included with others classified as Type I	1 in Phase III 1 in Phase V-2
no cases are included where subjects over or under performed the exercise during the PB since results were used to accept or reject the PB procedure	1 case where the subject under exercised and 1 case where the subject over exercised early during the PB is included since the model accounts for exercise PB	2 in Phase V-3
no cases included where VO_2 pk was estimated, leaving only 4 cases in Phase III and 3 in Phase IV for the model	68 cases where VO_2 pk was estimated, with 66 that qualified to be in the research model	6 in Phase III 62 in Phase IV
1 case that failed to complete a minimum of 230 min at 4.3 psia and later classified as no DCS was not included	1 case that failed to complete a minimum of 230 min at 4.3 psia and later classified as no DCS was not included	1 in Phase III
1 case that failed to complete a minimum of 230 min at 4.3 psia was not included	1 case that failed to complete a minimum of 230 min at 4.3 psia was not included	1 in Phase V-2
30 sec break in PB, with PB extended by 2 min was included	30 sec break in PB, with PB extended by 2 min was included	1 in Phase V-3
2 cases experienced a minor pressure transition at the beginning of the test, and were included	2 cases experienced a minor pressure transition at the beginning of the test, and were included	2 in Phase V-3
1 case where subject peddled ergometer faster than needed during initial warm-up plus polar heart watch had failed was included	1 case where subject peddled ergometer faster than needed during initial warm-up plus polar heart watch had failed was included	1 in Phase V-3

Table 6 is a summary of the number of exposures that finally qualified to be used to test the hypothesis about the seven PB protocols, and to be included in the NM and the RM. The incidence of DCS associated with these acceptable exposures serves as the observed outcome of the tests. The observed DCS outcome is later compared to the predicted outcome from the NM and the RM.

TABLE 6: Data for Test of Prebreathe Hypothesis and Model Data

Phase	Total n	Test of Hypothesis Data	Observed %TDCS* (DCS cases)	NM	Observed %TDCS* (DCS cases)	RM	Observed %DCS (DCS cases)
I	49	47	19.1^b (9)	47	19.1^b (9)	49^a	14.3 (7)
II	50	45	0 (0)	45	0 (0)	$47^{c,j}$	0 (0)
III	10	9	22.2 (2)	4	50.0 (2)	9^d	22.2 (2)
IV	65	56	14.3 (8)	3	0 (0)	$62^{e,f}$	12.9 (8)
V-1	10	9	33.3 (3)	9	33.3 (3)	9^g	33.3 (3)
V-2	4	3	33.3 (1)	3	33.3 (1)	3^h	33.3 (1)
V-3	50	48	14.6 (7)	48	14.6 (7)	50^i	14.0 (7)
Sum	238	217	30 DCS cases	159	22 DCS cases	229	28 DCS cases

* TDCS is DCS reported during and after an altitude exposure, a. two cases went long on PB, b. two cases of DCS reported after altitude exposure was complete, c. three went long on PB, one classified as ambiguous, d. one failed to complete 230 min and later classified as no DCS, e. eight went long on PB, f. one classified as ambiguous and failed to complete 230 min, two classified as ambiguous, g. one classified as ambiguous and failed to complete 230 min, h. one failed to complete 230 min, i. two had modified exercise profiles very early in the PB, j. two failed to complete 230 min due to DCS in DT.

The data in Table 7 for the RM and Table 8 for the NM reveal subtle trends that relate explanatory variables to the DCS outcome. Those with DCS are on average about four years older than those without DCS, and VO_2 pk in the older subjects with DCS is about 3 $mL*kg^{-1}*min^{-1}$ lower than in those without DCS. The tables are formatted such that the information associated with DCS outcome is at the top of each table. Since the presence of VGE and Grade IV VGE are also outcomes of the exposures, those data are included. Since the seven PB protocols are confounders and act as covariates, the PB and exercise components need to be managed in the multivariable statistical analysis to follow before any trends in these data can be confirmed. In this way, small differences due to age, gender, or VO_2 pk might rise to statistical significance in the model. Also notice that a greater percentage of females out of the total number of females have DCS compared to males, about 17% (9 / 54) for females in the data for the RM from Table 7 have DCS compared to 11% (19 / 175) of the males. The same trend is seen in the data for the NM, about 28% (11 / 39) of the females in Table 8 have DCS compared to 9% (11 / 120) for the males. It is likely that age will be a significant predictor in the RM while gender is a significant predictor in the NM, and VO_2 pk is important in both models based on the descriptive statistics in Tables 7 and 8.

TABLE 7. Summary Statistics for Explanatory and Outcome Variables in the RM

Phase	DCS	VGE	GIV VGE	AGE	SD	WT	SD	HT	SD	BMI	SD	VO$_2$ Pk	SD	SEX M F
I	7	7	2	32.1	9.4	69.2	12.0	170.3	12.5	23.8	2.8	37.5	5.6	4 3
II	0													
III	2	1	1	36.0	9.4	77.1	19.2	174.0	9.0	25.2	3.7	36.5	9.5	1 1
IV	8	7	3	32.1	7.6	84.9	12.3	182.4	5.9	25.5	3.2	41.7*	4.0	8 0
V-1	3	3	2	34.9	10.9	87.2	5.6	182.0	1.4	26.8	1.1	44.3	4.6	3 0
V-2	1	1	1	42.7	0	65.8	0	165.1	0	24.2	0	31.2	0	0 1
V-3	7	6	0	40.8	12.2	71.3	13.0	175.7	7.6	22.9	2.5	42.3	9.7	3 4
total	28	25	9	35.2	9.8	76.6	13.5	176.5	9.4	24.5	2.8	40.3!!	6.8	19 9
	No DCS													
I	42	17	0	28.9	7.3	76.2	13.7	176.7	9.6	24.2	3.0	39.2	7.3	31 11
II	47	14	3	31.6	9.0	77.4	15.2	176.6	7.3	24.6	3.7	41.6	7.1	38 9
III	7	0	0	28.2	6.3	81.4	6.2	178.4	4.2	25.5	1.7	42.3**	2.5	7 0
IV	54	17	4	29.7	7.6	75.8	12.5	176.0	8.8	24.4	3.2	40.8!	4.9	39 15
V-1	6	2	0	29.8	2.3	71.0	13.8	178.2	12.7	22.2	2.9	45.2	5.4	4 2
V-2	2	2	1	37.5	3.6	86.4	37.5	177.1	18.8	26.7	6.3	36.9	2.2	1 1
V-3	43	20	5	36.3	7.0	80.5	13.7	177.4	8.5	25.5	3.1	44.5	7.8	36 7
total	201	72	13	31.4	8.0	77.4	13.8	176.7	8.6	24.6	3.2	41.6!!!	6.8	156 45

* 8 of 8 had estimated VO$_2$ pk

** 5 of 7 had estimated VO$_2$ pk

! 52 of 54 had estimated VO$_2$ pk

!! 8 of 28 had estimated VO$_2$ pk

!!! 57 of 201 had estimated VO$_2$ pk

TABLE 8. Summary Statistics for Explanatory and Outcome Variables in the NM

Phase	DCS	VGE	GIV VGE	AGE	SD	WT	SD	HT	SD	BMI	SD	VO$_2$ Pk	SD	SEX M F
I	9*	8	2	29.8	9.3	68.0	11.3	169.4	11.0	23.6	2.9	35.4	6.9	4 5
II	0													
III	2	1	1	36.0	9.4	77.1	19.2	174.0	9.0	25.2	3.7	36.5	9.5	1 1
IV	0													
V-1	3	3	2	35.0	11.0	87.2	5.6	182.0	1.4	26.8	1.1	44.3	4.6	3 0
V-2	1	1	1	42.7	0	65.8	0	165.1	0	24.2	0	31.2	0	0 1
V-3	7	6	0	40.8	12.2	71.3	13.0	175.7	7.6	23.0	2.5	42.3	9.8	3 4
total	22*	19	6	35.1	10.8	72.4	12.7	173.3	9.4	24.0	2.7	38.7	8.3	11 11
	No DCS													
I	38	15	0	29.0	6.8	77.0	14.0	177.1	9.7	24.3	3.0	39.8	7.0	29 9
II	45	14	3	31.7	9.0	77.6	15.4	176.3	7.8	24.8	4.0	40.8	7.2	35 10
III	2	0	0	27.1	2.7	84.1	2.9	179.0	5.4	26.2	0.7	41.7	1.2	2 0
IV	3	1	1	41.8	12.0	82.6	4.2	182.9	7.5	24.8	3.1	43.4	6.1	3 0
V-1	6	2	0	29.8	2.3	71.6	13.8	178.2	12.7	22.2	2.9	45.2	5.4	4 2
V-2	2	2	1	37.5	3.6	86.4	37.5	177.1	18.8	26.7	6.3	36.9	2.2	1 1
V-3	41	19	5	36.2	7.1	81.2	13.6	177.8	8.5	25.5	3.1	44.3	7.3	35 6
total	137	53	10	32.5	8.2	78.5	14.5	177.3	8.8	24.8	3.4	41.8	7.2	109 28

* two cases of DCS in Phase I reported after the test

Exercise Prebreathe Model:

We must ultimately compute an ETR for each of the 159 records in the NM and 229 records in the RM. This ETR becomes the decompression dose for the LR model. The ratio of $P1N_2$ to P2 is the ETR, where $P1N_2$ is the calculated N_2 pressure after the ascent to altitude in a theoretical compartment with a variable half-time for N_2 pressure. Half-time is the time it takes to increase or decrease to one-half of the difference in the initial minus final condition, in our case N_2 pressure. Within four half-time periods about 94% of the difference in the initial minus final condition is achieved. The denominator of TR is P2, the ambient pressure after ascent. All of our depressurizations were to 4.3 psia since this is the operating pressure of the U.S. space suit.

Prebreathing 100% O_2 or O_2-enriched mixtures prior to an altitude exposure is often used to prevent DCS, so it is necessary to account for the use of O_2-enriched mixtures prior to the start of the altitude exposure. Equation 4 defines how $P1N_2$ is calculated. Following a change in N_2 partial pressure in the breathing mixture, 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:

$$P1N_2 = P_0 + (P_a - P_0) * (1 - \exp^{-k_i * t}), \qquad\qquad \text{Eq. 4}$$

where $P1N_2$ = the N_2 partial pressure in the tissue after "t" minutes, P_0 = initial N_2 partial pressure in the compartment, P_a = ambient N_2 partial pressure in breathing mixture, exp = base of natural logarithm, and t = time at the new P_a in minutes. The tissue rate constant k_i is related to the tissue N_2 half-time (t1/2) for N_2 pressure in a compartment. The "k" is equal to 0.693 / t1/2, where t1/2 is the half-time for N_2 partial pressure in the i_{th} minute compartment and 0.693 is the natural logarithm of two. 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 about 11.0 psia, a convention also used in some models for hyperbaric decompression. 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. 4 simple. We chose to avoid the additional complexity of calculating alveolar N_2 pressure (indirectly with the alveolar O_2 equation) or measuring alveolar N_2 pressure in those tests where a mixture of 26.5% O_2 and 73.5% N_2 was breathed while at 10.2 psia.

Functions that Define Half-Time Shift with Exercise:

The following are the functional structure of three equations, one of which will eventually define the best relationship between k_i and $mL*kg^{-1}*min^{-1}$ to use in Eq. 4:

$$k_1 = \lambda_1 * mL*kg^{-1}*min^{-1} + 0.0019254, \qquad\qquad \text{Eq. 5}$$

where the slope term λ_1 is estimated by trial and error and additional parameters in the LR are estimated using maximum likelihood.

Figure 4 shows three examples of Eq. 5. Only three of an infinite number of isopleths are shown, where $\lambda_1 = 0.0003888$ for the top curve, 0.0002888 for the middle curve, and 0.0001888 for the bottom curve. The best-fit to the DCS data could be a linear relationship between k and $mL*kg^{-1}*min^{-1}$ such that an incremental change in $mL*kg^{-1}*min^{-1}$ is associated with an incremental change in half-time compartment. Only a single slope term will be the best to define the change in half-time compartment through the exercise PB segments defined for each of the subjects in Phases I - V-3.
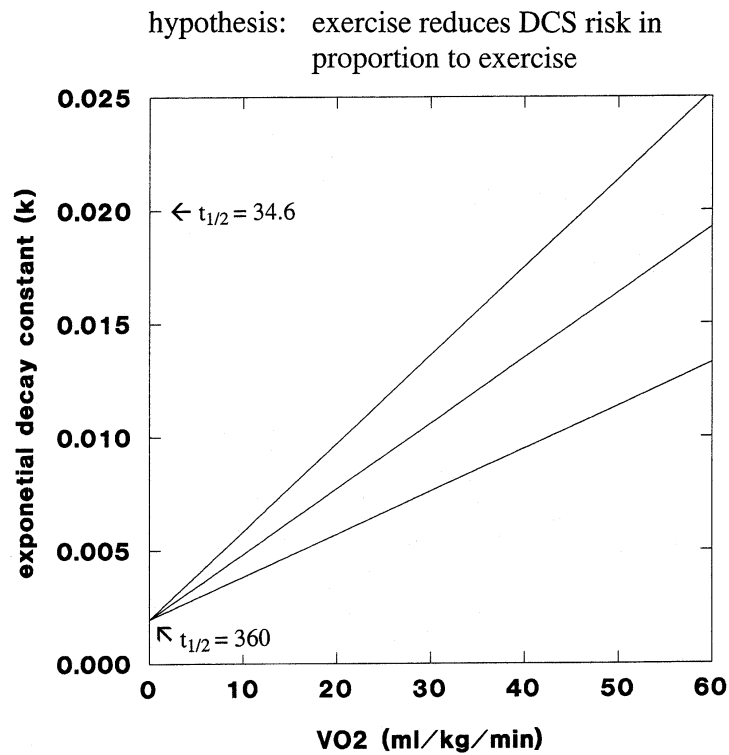
Figure 4. Linear relationship between k and $mL*kg^{-1}*min^{-1}$, which is the normalized VO_2 rate. The equation for the line is $k_1 = \lambda_1 * mL*kg^{-1}*min^{-1} + 0.0019254$, where the slope term is estimated by trial and error. When $mL*kg^{-1}*min^{-1} = 0$, then $k_1 = 0.0019254$ or 360 t1/2 through t1/2 = ln2 / k_1.

$k_2 = [(1 / \exp(-\lambda_2 * mL*kg^{-1}*min^{-1})) / 519.37]$,   Eq. 6

where the slope term λ_2 is estimated by trial and error.

Figure 5 shows three examples of Eq. 6. Only three of an infinite number of isopleths are shown, where $\lambda_2 = 0.045$ for the top curve, 0.040 for the middle curve, and 0.035 for the bottom curve. The best fit to the DCS data may be a nonlinear relationship between k and $mL*kg^{-1}*min^{-1}$ such that light exercise is not as beneficial has heavy exercise. Only a single slope term will be the best to define the change in half-time compartment through the exercise PB segments defined for each of the subjects in Phases I - V-3.
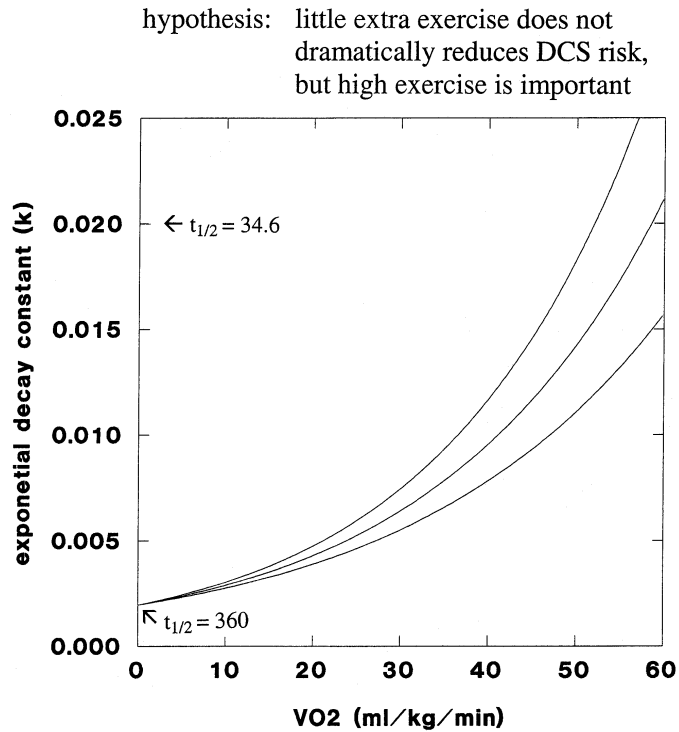
Figure 5. Nonlinear relationship between k and $mL*kg^{-1}*min^{-1}$ with a slow initial response in the exponential decay constant with a change in normalized VO_2 rate. The equation for the curve is $k_2 = [(1 / \exp(-\lambda_2 * mL*kg^{-1}*min^{-1})) / 519.37]$, where the slope term is estimated by trial and error. When $mL*kg^{-1}*min^{-1} = 0$, then $k_2 = 0.0019254$ or 360 t1/2 through t1/2 = ln2 / k_2.

$k_3 = ((1 - \exp(-\lambda_3 * mL*kg^{-1}*min^{-1})) / 51.937) + 0.0019254,$ Eq. 7

where the slope term λ_3 is estimated by trial and error.

Figure 6 shows three examples of Eq. 7. Only three of an infinite number of isopleths are shown, where $\lambda_3 = 0.25$ for the top curve, 0.15 for the middle curve, and 0.05 for the bottom curve. The best-fit to the DCS data may be a nonlinear relationship between k and $mL*kg^{-1}*min^{-1}$ such that light exercise has a dramatic beneficial effect on decreasing the half-time compartment, but additional heavy exercise reaches a point of diminishing returns. Only a single slope term will be the best to define the change in half-time compartment through the exercise PB segments defined for each of subjects in Phases I - V-3.
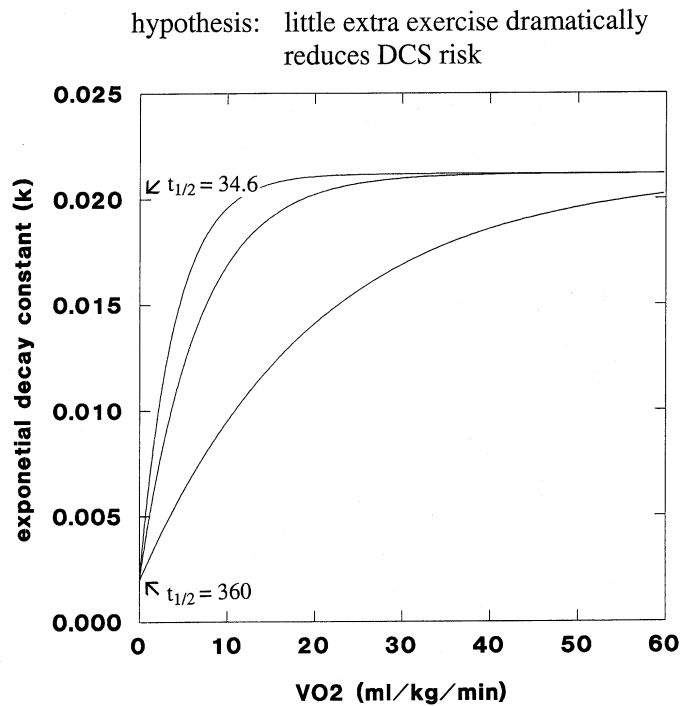
Figure 6. Nonlinear relationship between k and $mL*kg^{-1}*min^{-1}$ with a rapid initial response in the exponential decay constant with a change in normalized VO_2 rate. The equation for the curve is $k_3 = ((1 - \exp(-\lambda_3 * mL*kg^{-1}*min^{-1})) / 51.937) + 0.0019254$, where the slope term is estimated by trial and error. When $mL*kg^{-1}*min^{-1} = 0$, then $k_3 = 0.0019254$ or 360 t1/2 through $t1/2 = \ln 2 / k_3$.

Logistic Regression Model:

Probabilistic modeling of DCS data requires four items: a) a data set that consists of a dichotomous response variable and one or more explanatory variables, b) a probability function that structures the model such that the outcome is a calculated probability between zero and one, c) a mechanistic model that is an expression of dose, and d) a parameter-estimation routine on a computer that uses maximum likelihood.

The logistic equation serves as our probability function, and has three characteristics. First, it is ideal in applications where the response variable is binary since the expected value of "Y" given the value of "x", symbolized as E(Y|x), must be bounded between zero and one. The conditional mean in this application is written as P(DCS), or more formally $\pi^\wedge(x)$. Second, the change in $\pi^\wedge(x)$ per unit change in "x" becomes progressively smaller as the conditional mean gets closer to zero or one. Third, the binomial, not the normal, distribution describes the distribution of errors when this equation is used with binary response data. As a result, the error has a distribution with mean zero, and variance that is not constant across all levels of the independent variable but equals [P(DCS) * (1 - P(DCS))]. There is no requirement of homoscedasticity (equality of variances) in LR.

The form of the logistic equation with only one independent variable is:

$$P(DCS) = \exp(B_0 + B_1 x) / (1 + \exp(B_0 + B_1 x)) \qquad \text{Eq. 8}$$

where B_0 is the intercept term, and $B_1 x$ is the slope for variable "x" on a plot of log of odds vs. "x". In this application, the log of odds, or logit, is ln[P(DCS) / (1 - P(DCS))].

The logit transformation is a transformation of P(DCS) that is central to the application of LR. The logarithmic transformation linearizes the equation. The Logit module of SYSTAT®

(48,60) performs this transformation to calculate the log of odds, which is important in the calculation of the odds ratio, a measure of association between the independent and dependent variable. The logit transformation in this application is:

$$g(x) = \ln[\, P(DCS) / (1 - P(DCS))] = B_0 + B_1 x \qquad \text{Eq. 9}$$

and again, $\ln[\, P(DCS) / (1 - P(DCS))]$ is called the log of odds or logit.

This transformation is important because the logit, $[g(x)]$, is linear in its parameters, may be continuous, and may range from $-\infty$ to $+\infty$, depending on the range of "x". The logit is the log of the estimated odds of DCS given a value for "x" after B_0 and $B_1 x$ are found by maximizing the likelihood function.

If there are "n" explanatory variables, x_1, x_2, ... ,x_n, the univariate logistic model is expanded to a multivariate logistic model as follows:

$$P(DCS)[x_1, x_2, ... ,x_n] = \exp(B_0 + B_1 x_1 +...+ B_n x_n) / (1 + \exp(B_0 + B_1 x_1 +...+ B_n x_n)) \quad \text{Eq. 10}$$

and the logit becomes:

$$\ln[P(DCS) / (1 - P(DCS))] = B_0 + B_1 x_1 + ... + B_n x_n \qquad \text{Eq. 11}$$

Exponentiating the logit provides the odds of DCS, and the odds divided by $1 +$ odds gives the P(DCS). Note that it is not possible to draw a single dose-response curve from results of a multivariate LR. All but one covariate must be set constant to show how the P(DCS) changes through the range of the single independent variable of interest.

Now, for our specific case. The ETR after exercise PB is the dose for the LR. ETR is $P1N_2 / 4.3$. The numerator is computed using Eq. 6, for example, as $k_2 = [(1 / \exp(-\lambda_2 *$ $mL*kg^{-1}*min^{-1}) / 519.37]$, where k_2 is used in Eq. 4 to compute $P1N_2$ across the exercise PB details for each subject once λ_2 is selected by trial and error. This means that three components make up the description of each PB interval performed by a subject: the elapsed time of the exercise during PB, the percentage of VO_2 pk as $mL*kg^{-1}*min^{-1}$ for the exercise during PB, and the P_a for Eq. 4 , usually zero ppN_2 for a 100% O_2 PB but would be 7.5 ppN_2 when the PB was continued at 10.2 psia while the subject breathed 26.5% O_2. Recall that P_a is ambient N_2 partial pressure in breathing mixture. Now there were as few as five and as many as 32 intervals that defined the exercise PB to cover the seven tested exercise PB conditions (see Table 3). Intervals of rest were necessarily included, and 9.5% VO_2 pk was used for O_2 consumption during rest. Each of these intervals for each subject across all tests is assigned a half-time based on the value of λ used in either Eqs. 5,6, or 7. There can only be one best half-time for each interval depending on only one best λ value from either Eqs. 5,6, or 7. The outcome variable, DCS and no DCS, was used to find the value of λ from Eqs. 5,6, or 7 that best optimized the ETR expression of dose in the LR to the DCS outcome, using maximum likelihood optimization.

The denominator of ETR is a constant, 4.3 psia. So the simplest form of the LR is:

$$P(DCS) = \exp(B_0 + B_1 * (P1N_2 / 4.3)) / (1 + \exp B_0 + B_1 * (P1N_2 / 4.3))), \qquad \text{Eq. 12}$$

where the values of B_0, B_1, and λ for the RM and the NM are estimated through the Logit module of SYSTAT®. Other explanatory variables such as age, sex, Body Mass Index (BMI), etc., are included to expand this basic LR model if they statistically contribute to the description of the DCS outcome.

An advantage of LR is the ability to include many variables, some of which may be on different measurement scales. When an explanatory variable is dichotomous it is inappropriate

to include it in the model as if it were a continuous, interval-scaled variable. Numbers used to represent various levels are merely identifiers, and have no numeric significance. Therefore, dummy variables are used to deal with our only polytomous categorical variable, the seven PB protocols. A polytomous variable has more than two categories. Converting a polytomous variable into a set of dummy variables is essentially creating n_c - 1 dichotomous covariates where n_c is the number of categories in the covariate. This variable was automatically converted by the computer to dummy variables for regressions that include them. But the results were very poor with this approach and no results are presented. Sex is the only dichotomous explanatory variable evaluated. A dichotomous covariate is coded as zero or one and treated as interval scaled. The remaining covariates are continuous, ordinal scaled.

Measures of Goodness of Fit:

An important aspect of probabilistic modeling is to determine how confident one can be in an estimate of P(DCS) once the optimum parameters in a model are found. It is important to emphasize the distinction between the best fit of the model to the data and the goodness of fit of the model. With least squares or maximum likelihood, a function is optimized to the data regardless of the strength of the relationship between the independent and dependent variables. Goodness of fit, after obtaining the model with the best fit, is a measure of the agreement between the predicted outcome and the observed outcome. Without a measure of goodness of fit it is possible to be unjustifiably confident in the estimate of P(DCS).

In general, assessing the goodness of fit revolves around an overall summary measure of distance between actual (y_i) and estimated ($y\verb|^|_i$) outcomes, and an examination of the individual components (y_i - $y\verb|^|_i$) of the summary statistics to identify outliers. The circumflex " ^ " denotes an estimate of the function. A model "fits" if summary measures of distance are small, and the contribution of each pair (y_i, $y\verb|^|_i$) to these summary measures is unsystematic. In linear least squares regression, the sum of the differences between observed "y" and predicted "y^", the

residual, is a measure of agreement, and the goodness-of-fit statistic is the Coefficient of Determination (R^2). The Coefficient of Determination is interpreted as the fraction of the variance in "y" predicted by "x". However, when the dependent variable is dichotomous and the data is fitted with a probability model, the difference between observed and predicted is not the same residual as defined in a linear least squares regression. In this case, one of two possible outcomes is observed, a yes (1) or no (0), but the predicted is a probability between zero and one.

The two summary measures of goodness-of-fit used here are: Hosmer-Lemeshow Goodness-of-Fit Test and One-Sample χ^2 Test, both of which provide an easily interpretable value that can be used to assess the fit.   There are no quantitative methods available in the Logit module of SYSTAT® that help the user accept or reject a model based on the goodness of fit. Therefore, the user ultimately decides subjectively if the estimates of P(DCS) from the fitted model are useful. We also compare the LL of the best-fit NASA and Research continuous models to the null and discontinuous models.   The difference in the LL number between the best-fit mechanistic model and the null and discontinuous models is used to assess goodness of fit of the NM and RM. The null model and discontinuous model are covered in the Results when the best fit NM and RM are described.

A high goodness of fit is not a validation of the model. It is expected that a model optimized to a set of training data will return an acceptable goodness of fit. Model validation is a separate process. Traditional approaches often involve randomly selecting a subset of data from the training set and comparing predicted outcome from the model to observed outcome in the subset. Another approach is to compare model predictions to outcomes from new data not used to optimize the initial model. Neither the NM nor the RM is validated as part of this report. Validation of the models is a subject for future work.

Results

Test of Hypothesis Data:

Before showing the results of the regressions, we show in Table 9 a summary of the results used in the test of hypothesis for the seven PBs. Phases I through V-3 were not designed to provide a range of data for a probability model. The analysis using multivariate statistical regression presents itself due to the complexity of the tested PBs. In all tests the goal was to only accept a PB option that produced $\leq$ 15% Type I DCS and $\leq$ 20% Grade IV VGE, with no Type II DCS and preferably in a sample of at least 50 subjects. Type I DCS include "pain only" symptoms in the limbs while Type II DCS includes signs and symptoms linked to disruptions in the cardiopulmonary and neurological systems. Grade IV VGE was defined earlier. We imposed that the accept condition for the PB had to meet or exceed 95% confidence. This means that the observed DCS and Grade IV VGE in a trial of 50 subjects could not exceed 6% and 10%, respectively. Table 9 shows that only Phase II met these accept conditions. Both Phase III and Phase V-2 had a case of Type II DCS, and no further testing was done.

TABLE 9: Data for Test of Prebreathe Hypothesis

Phase	Total n	Test of Hypothesis Data	Observed %DCS (n)	Observed %VGE (n)	Observed %Grade IV VGE (n)
I	49	47	19.1[*] (9)	48.9 (23)	4.2 (2)
II	50	45	0 (0)	31.1 (14)	6.6 (3)
III	10	9	22.2 (2)	11.1 (1)	11.1 (1)
IV	65	56	14.3 (8)	41.0 (23)	12.5 (7)
V-1	10	9	33.3 (3)	55.5 (5)	22.2 (2)
V-2	4	3	33.3 (1)	100 (3)	66.6 (2)
V-3	50	48	14.6 (7)	52.1 (25)	10.4 (5)
Sum	238	217	30 DCS cases	94 VGE cases	22 Grade IV VGE cases

* two cases of DCS reported after altitude exposure was completed

Research Model:

Table 10 shows the results of optimizing nested models to the 229 exposures in the RM that resulted in 28 cases of DCS in seven tests. The first model in Table 10 is the null model. The null model is a constant-probability model based on the mean DCS incidence for all the individuals in the data set, 12.2% in this case. The null model has a single degree of freedom, and the LL necessarily represents a poor fit to a response variable; all explanatory variables are assumed irrelevant to the outcome. The null model returned a LL number of 85.05, using absolute value for LL. In the same data set, the LL from a discontinuous model is defined as the best, or perfect LL based on the assertion that the DCS incidence in each test is the true DCS incidence. The LL for the discontinuous model is 76.58. Equation 13 is used to compute the LL for the discontinuous model:

$$LL = \sum_{i=1}^{n} \ln [(1 - c_i)^{nodcs_i} * (c_i)^{dcs_i}] \qquad \text{Eq. 13}$$

where "n" is the number of tests, c_i is the fraction of subjects with DCS in test "i", $nodcs_i$ is the number of subjects without DCS in test "i", and dcs_i is the number of subjects with DCS in test "i". Equation 13 uses the number of subjects in a particular test with and without DCS, and the incidence of DCS in the test. The discontinuous model has as many degrees of freedom as there are tests, seven in this case. A continuous model like the RM based on theory would not necessarily predict the observed DCS incidence, so the summed LL would always exceed the summed LL for the discontinuous model.

Accounting for the use of O_2 during the PB with a 360 min half-time compartment in a two-parameter LR reduced the LL to 81.61. So TR based on a 360 min half-time compartment at the start of exercise at 4.3 psia is helpful. However, exercise during the PB is expected to accelerate N_2 washout, so a model with the provision to change the half-time compartment over an interval of exercise activity that is functionally linked to the percentage of VO_2 pk in that

same interval is expected to be an improvement. The LL for the ETR model did decrease to 80.17 when λ_2 from Eq. 6 was 0.025. The same improvement in LL did not occur when λ_1 from Eq. 5 or λ_3 from Eq. 7 were evaluated over a wide range of values (results not shown). So the DCS outcome in the final RM, and also the NM, are best described with a model that says modest exercise intensity as defined by the percentage of VO_2 pk is helpful, but greater exercise intensity is best if the goal is to reduce the risk of DCS with exercise during PB. Figure 5 shows this functional relationship for three examples of λ_2.

Due to a limitation in the automated SYSTAT® process to optimize these models, the value of λ_2 was obtained in a trial and error fashion where new values were tried after each model optimization until there was no further improvement (decrease) in the LL. The ETR model with the LL of 80.17 is a three-parameter model since there are three degrees of freedom in which to optimize the observed incidence of DCS with the predicted incidence of DCS. But only the B_0 and B_n coefficients of this model have a standard error, and therefore computed p-values. This deficiency should be resolved in the next update to the model. This same limitation is the reason that only a best estimate of DCS risk is provided, without the ability to compute a confidence interval for the best estimate of P(DCS).

The improvement of the ETR model continued as useful explanatory variables were added. The addition of age and sex decreased the LL to 77.36, but sex was not significant enough to remain in the model (p = 0.49). The best model located at the bottom of Table 10 accounts for exercise during the PB and the age of the subject, and this model is called the RM. The positive sign on the coefficient for age in the RM means that the P(DCS) increases when age increases. The odds ratio for age was 1.055, with 1.008 to 1.103 as the lower and upper 95% bounds on the odds ratio. In this case, the odds ratio is the ratio of odds of DCS per year to the odds of DCS for a particular age. An example is helpful. The odds of DCS increased from 0.019 to 0.033 for a 10 year increase in age from 30 to 40 given an ETR of 1.8. Since the P(DCS) = odds / 1 + odds, the P(DCS) in this example increased from 1.9% to 3.2% for a 10 year increase in age.

A LL of 77.58 for the RM is a statistically significant improvement based on the Likelihood Ratio Test over the null model, the model with a constant 360 min half-time tissue compartment, and a model that just accounted for exercise during the PB. The Likelihood Ratio Test determines if the inclusion of an additional degree of freedom (an additional fitted parameter) significantly improves a particular model. It is the preferred method for hypothesis testing when using maximum likelihood. The test involves comparing the LLs of two models, the restricted and unrestricted, fitted to the same set of data. A restricted model can contain a single parameter, called the null model. 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, or other restricted model, by testing the hypothesis that the additional coefficient in a model is equal to zero.

The value of the Likelihood Ratio statistic is calculated as two times the difference in the LL between the unrestricted and restricted models, which are different by at least one estimated parameter. 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 χ^2 p-value. A p-value less than 0.05 is generally taken to mean that the null hypothesis should be rejected, i.e., that the additional parameter is not equal to zero.

In addition to information on the parameter estimates, there is information on the goodness of fit of the models. For example, the ETR model with a LL of 80.17 shows a p-value of 0.31 based on the Hosmer-Lemshow statistic. The Hosmer-Lemeshow Goodness-of-Fit test provides a calculated statistic (C) and degrees of freedom for the logistic model. The distribution of the statistic C is approximated by the χ^2 distribution with g - 2 degrees of freedom where "g" is the number of groups, usually ten. The number of groups is based on the values of the estimated probabilities, and is automatically calculated in the Logit module of SYSTAT®. The groups form a Deciles of Risk Table that is part of the output from the Logit module. The information in each cell of the table quantifies how well the model predicts the observations in a specific region of the data. The C statistic is used here to summarize the goodness of fit of the

model to the entire set of data. The p-value from a χ^2 table for the C statistic is provided, and the larger the p-value, the better the goodness of fit.

TABLE 10: Seven Research Model Results

Research Model	N = 229	DCS = 28 cases	
Null model LL	85.05	12.2% DCS	
Discontinuous model	76.58		
TR360 model LL	81.61		
ETR model LL	80.17		
PARAMETER	ESTIMATE	STANDARD ERROR	P-VALUE
constant	-29.11	8.718	0.001
ETR	14.11	4.513	0.002
λ_2	0.025	not available	not available
Hosmer-Lemshow C statistic	C = 3.549	3 degrees freedom	0.31
ETR+age+sex LL	77.36		
PARAMETER	ESTIMATE	STANDARD ERROR	P-VALUE
constant	-30.41	9.24	0.001
ETR	13.96	4.70	0.003
age	0.055	0.023	0.018
sex	-0.32	0.473	0.49*
λ_2	0.025	not available	not available
Hosmer-Lemshow C statistic	C = 4.45	5 degrees freedom	0.48
ETR+sex LL	80.09		
PARAMETER	ESTIMATE	STANDARD ERROR	P-VALUE
constant	-28.19	9.01	0.002
ETR	13.71	4.62	0.003
sex	-0.192	0.46	0.68*
λ_2	0.025	not available	not available
Hosmer-Lemshow C statistic	C = 4.99	4 degrees freedom	0.29
ETR+age LL	**77.58**		
PARAMETER	ESTIMATE	STANDARD ERROR	P-VALUE
constant	**-31.717**	9.000	0.000
ETR	**14.55**	4.600	0.002
age	**0.053**	0.023	0.021
λ_2	**0.025**	not available	not available
Hosmer-Lemshow C statistic	C = 3.851	5 degrees freedom	0.57

* parameter not significant enough to remain in model

Table 11 shows the comparison between the observed and predicted DCS outcome using the best-fit RM from the bottom of Table 10. The RM over predicted the results for Phase II, but either over or under predicted the remaining results. Therefore, the RM is not biased high or low. Besides a visual impression about how well the RM predicts the observed DCS, these data are also used in a One-Sample χ^2 Test as a second means to quantify goodness of fit. The test compares an observed distribution to a theoretical one. The null hypothesis is that there is no difference between the distributions. In the case where estimated always equals observed, the sum of all χ^2 values computed for each of the seven tests is zero. A p-value greater than 0.05 indicates that there is no statistical difference between the two sets of outcomes, the ones observed and ones predicted with a model. The RM gave a χ^2 of 6.25, and with three degrees of freedom (7 tests – 4 degrees of freedom in RM) the p-value was 0.10.

TABLE 11: Observed versus Predicted DCS with Research Model

Phase	n	mean age	estimated oxygen consumption (l)	Observed %DCS	Predicted %DCS*
I	49	29.41	76.5 ± 20.1	**14.3 (7)**	**12.8**
II	47	31.66	88.1 ± 20.7	**0 (0)**	**6.3**
III	9	29.94	60.2 ± 6.2	**22.2 (2)**	**11.5**
IV	62	30.0	66.7 ± 12.3	**12.9 (8)**	**9.3**
V-1	9	31.53	78.4 ± 15.5	**33.3 (3)**	**34.3**
V-2	3	39.23	62.0 ± 28.5	**33.3 (1)**	**55.4**
V-3	50	36.96	92.5 ± 22.2	**14.0 (7)**	**9.5**

* prediction based on model with age included

NASA Model:

Table 12 shows the results of optimizing nested models to the 159 exposures on the NM that resulted in 22 cases of DCS in seven tests. Note that two cases of DCS in Phase I were reported after the conclusion of the test. These cases are included in the NM, but not the RM. Again, the LL numbers for the null and discontinuous models are shown to give the worst and best fit to these data. As before with the description of the RM, the LL improved as exercise during the PB is accounted for by fitting the λ_2 value from Eq. 6, and by expanding the LR to include other helpful explanatory variables. The best-fit NM required a λ_2 value of 0.030. In these data, sex and not age was selected as a variable that improved the description of the DCS outcomes. The negative sign on the coefficient for sex in the NM means that the P(DCS) is reduced when sex is male. The odds ratio for sex was 0.355 with 0.133 to 0.945 as the lower and upper 95% bounds on the odds ratio for sex. Explaining the odds ratio for sex is easier than for age in the RM since sex is binary while age is on a continuous scale. In this case, the odds ratio is the ratio of odds of DCS for sex = 1 to the odds for sex = 0. Because of our convention to code male = 1 and female = 0, the smaller the odds ratio, the stronger the effect. A person decreases the odds for DCS by a factor of about three (1 / 0.355) when sex is male. An example is helpful. The odds increase from 0.030 to 0.085 if gender is female and ETR is 1.8 for this example. Odds of DCS converts to P(DCS) through the expression odds / 1 + odds, so in this example the P(DCS) increases from 2.9% to 7.8% if gender is female and ETR is 1.8. The best-fit NM at the bottom of Table 12 had a p-value of 0.70 from the Hosmer-Lemshow C statistic, indicating a good fit of the model to the data.

TABLE 12: Seven NASA Model Results

NASA Model	N = 159	TDCS* = 22 cases	
Null model LL	63.91	13.8% TDCS	
Discontinuous model	53.29		
TR360 model LL	60.39		
ETR model LL	58.36		
PARAMETER	ESTIMATE	STANDARD ERROR	P-VALUE
Constant	-30.02	8.81	0.000
ETR	14.80	4.59	0.001
λ_2	0.030	not available	not available
Hosmer-Lemshow C statistic	C = 0.834	4 degrees freedom	0.93
ETR+age LL	57.32		
PARAMETER	ESTIMATE	STANDARD ERROR	P-VALUE
constant	-32.23	9.187	0.000
ETR	15.29	4.72	0.001
age	0.038	0.026	0.141**
λ_2	0.030	not available	not available
Hosmer-Lemshow C statistic	C = 5.518	5 degrees freedom	0.35
ETR+age+sex LL	54.83		
PARAMETER	ESTIMATE	STANDARD ERROR	P-VALUE
constant	-28.18	9.68	0.004
ETR	13.41	4.95	0.007
age	0.047	0.027	0.085**
sex	-1.158	0.51	0.024
λ_2	0.030	not available	not available
Hosmer-Lemshow C statistic	C = 8.851	6 degrees freedom	0.18
ETR+sex LL	**56.28**		
PARAMETER	ESTIMATE	STANDARD ERROR	P-VALUE
constant	**-25.56**	9.30	0.006
ETR	**12.83**	4.83	0.008
sex	**-1.037**	0.50	0.038
λ_2	**0.030**	not available	not available
Hosmer-Lemshow C statistic	C = 2.997	5 degrees freedom	0.70

* two cases of DCS in Phase I reported after test
** parameter not significant enough to remain in model

Table 13 shows that the NM also over predicted the results from Phase II, just like the RM in Table 11. The p-value from the One-Sample χ^2 test was 0.014 given a computed χ^2 of 10.62 with three degrees of freedom, which indicates the NM has a poorer goodness of fit compared to the RM using this statistic.

TABLE 13: Observed versus Predicted DCS with NASA Model

Phase	n	mean age	gender (% male)	estimated oxygen consumption (l)	Observed %TDCS	Predicted %TDCS**
I	47	29.19	0.70	76.5 ± 20.5	**19.1* (9)**	**16.0**
II	45	31.76	0.78	86.1 ± 20.2	**0 (0)**	**7.5**
III	4	31.57	0.75	57.3 ± 8.6	**50.0 (2)**	**15.5**
IV	3	41.80	1.00	75.2 ± 9.0	**0 (0)**	**9.6**
V-1	9	31.53	0.78	78.4 ± 15.5	**33.3 (3)**	**30.6**
V-2	3	39.23	0.33	62.0 ± 28.5	**33.3 (1)**	**53.4**
V-3	48	36.92	0.79	92.7 ± 21.8	**14.6 (7)**	**7.4**

* two cases of DCS in Phase I reported after test
** prediction based on model with sex included

In summary, we exploited all the otherwise acceptable data in the case of the RM by first estimating an important explanatory variable, the VO_2 pk, in about ¼ of the data. A more conservative approach was taken with the NM in that only data with measured VO_2 pk was evaluated. Each model has a similar ability to describe the DCS outcome. The RM is based on the most data, and predicts closer to the observed outcomes in seven tests. But we are less confidence in the estimate of DCS risk since 65 of the 229 records used in the model had an estimate of VO_2 pk. The alternative model based on 159 records does not predict as well, but we are more confident in the prediction since all the critical VO_2 pk data was measured. Figure 7 reiterates the point that the λ_2 value for the NM and RM are similar. Figures 8 and 9 are about the applications of the RM and NM. The user can get an appreciation for the change in DCS risk given a particular ETR and the age of the subject using Fig. 8. Figure 9 shows that for a given ETR in the NM, the risk for DCS is greater if you are female.
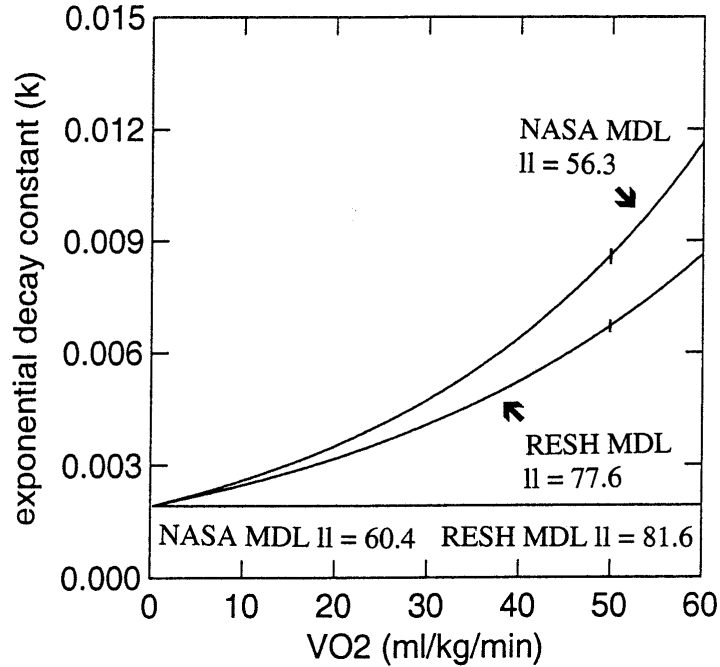
Figure 7. Best nonlinear relationship between k and $mL*kg^{-1}*min^{-1}$ for the NM and the RM compared to a model with a constant 360 min half-time compartment. The equation for the curves are $k_2 = [(1 / exp(-\lambda_2 * mL*kg^{-1}*min^{-1})) / 519.37]$, where the slope term λ_2 is 0.030 for the NM and 0.025 for the RM. At a very high O_2 consumption of 50 $mL*kg^{-1}*min^{-1}$ the half-time compartment has decreased from 360 min to 81 min for the NM and 99 min for the RM. The decrease in LL from the constant compartment model to a variable compartment model with exercise during PB is statistically significant for both the NM and RM.
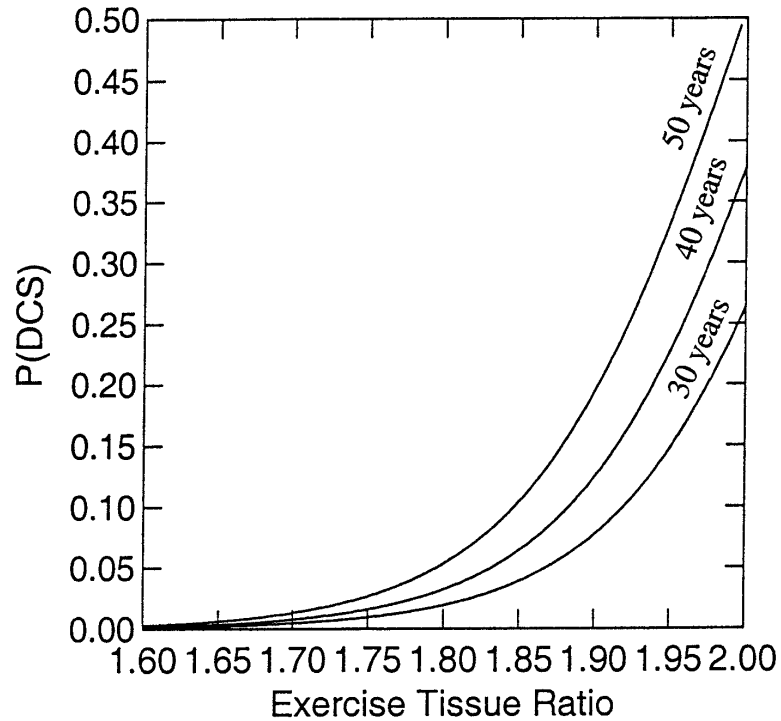
Figure 8. RM that shows P(DCS) as a function of ETR and age. As simulated age increases from 30 to 40 to 50 years, the P(DCS) for a given ETR increases. Gender was not an explanatory variable in these data, but 76.4% of 229 exposures were with males. The average age from Phase I through V-3 was 31.9 years $\pm$ 8.3 SD. Recall, that these estimates only apply to people who do similar exercise during PB and while at 4.3 psia as was done in the actual testing. These subjects were all semi-recumbent during the PB and while at altitude as a means to prevent ambulation.
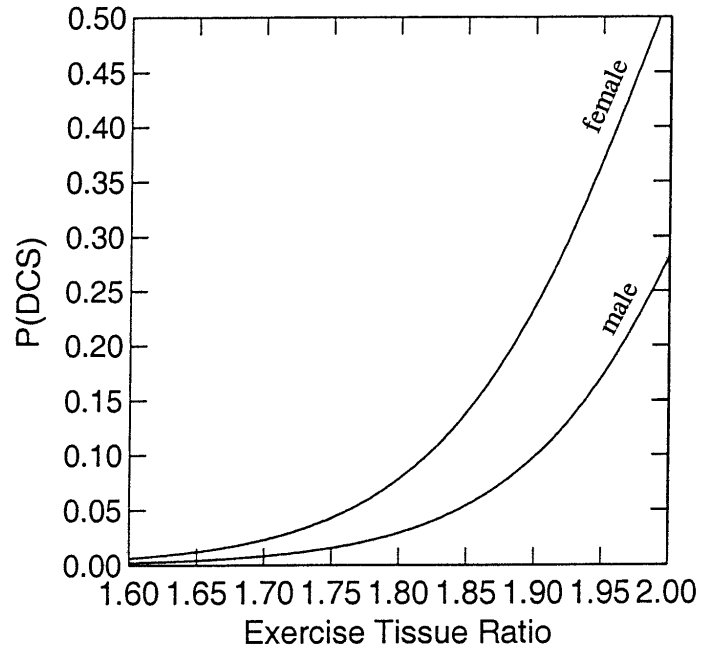
Figure 9. NM that shows P(DCS) as a function of ETR and gender. A female has a higher P(DCS) than a male at any given ETR. Age was not an explanatory variable in these data, but the average age was 32.8 years $\pm$ 8.6 SD. There was 75.5% male participation from Phase I through V-3 in the 159 exposures that comprise this set of data. Recall, that these estimates only apply to people who do similar exercise during PB and while at 4.3 psia as was done in the actual testing. These subjects were all semi-recumbent during the PB and while at altitude as a means to prevent ambulation.

Summary of VGE Results:

This report is about the risk of DCS at 4.3 psia after exercise PB, but a large amount of VGE data were collected. The VGE data are not described in detail, but only in a brief summary. Figure 10 shows how the fraction of VGE detected in the pulmonary artery changed through time for tests where enough data were collected to justify this analysis (Phases I, II, IV, and V-3). The x-axis is time in epochs when VGE data were collected. An epoch represents 16 min of time. The x-axis shows the fraction of VGE from the combined left and right legs (lower body). For example, if there were 48 measurements in the left leg and 48 measurements in the right leg at epoch 3, and VGE of any grade appeared five times in the left leg and six times in the right leg, then the fraction of lower body VGE for epoch 3 is 11 / 96 = 11.4%, and so on. The mean DCS times $\pm$ SD are shown in relation to the changing VGE fraction through time. There is no mean DCS time for Phase II since there was no DCS. The mean DCS time is statistically longer for Phase V-3 compared to Phase IV, 139 versus 87 min, p = 0.04 by unpaired t-test. The curves in Fig. 10 are just descriptive; we make no attempt to determine if there is a statistical difference between any curve. The details of the exercise PB for Phase V-3 and Phase IV are provided in the Appendix for those who wish to attribute the difference in DCS time to some aspect of the exercise during the PB.

Fraction of VGE from the Lower Body in Test of
Hypothesis Data from
Phase I (n=47), Phase II (n=45), Phase IV (n=56),
and Phase V-3 (n=48)
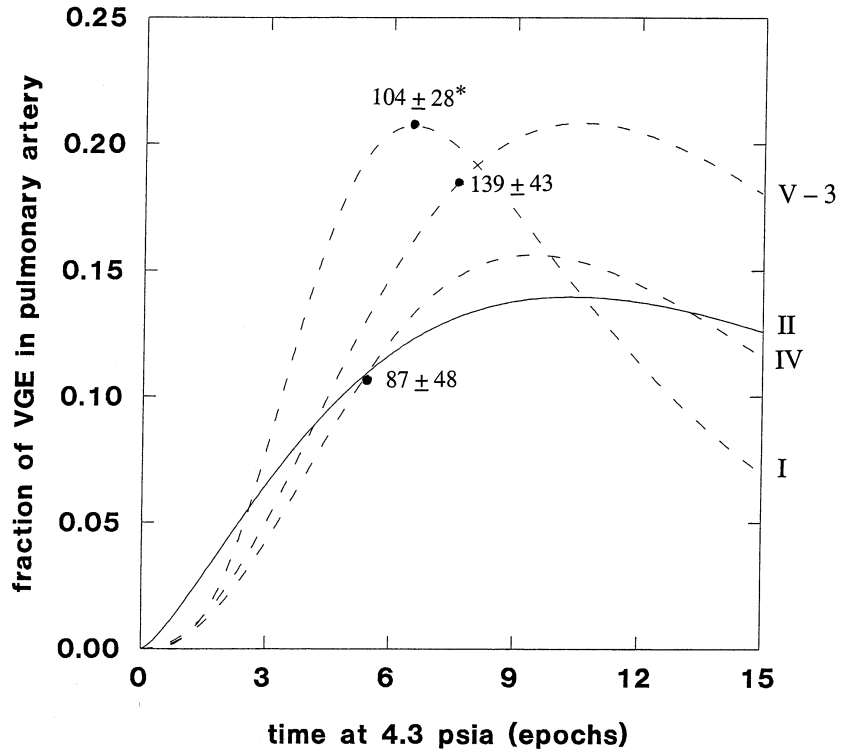
* two cases of DCS after test in Phase I not part of mean DCS time.
Difference in mean DCS time between Phase IV and Phase V-3 significant
with unpaired t-test (p=0.04)

Figure 10. The change in VGE incidence in the lower body through time. Bubbles appear in the pulmonary artery shortly after ascent to 4.3 psia at the conclusion of the exercise PB protocols in Phases I, II, IV, and V-3. Notice that the mean time to report DCS symptoms appears near the point of greatest VGE occurrence.

Order of Ergometry and VGE Latency Time:

The implementation of the ergometry exercise PB on the ISS requires that the first EVA astronaut start the ergometry while the second astronaut starts a resting PB. After 10 – 15 min, the second astronaut starts the ergometry, and then both complete the balance of the PB along the same time line. A similar situation was present in our testing of the exercise PB since there were often three subjects per test but only two sets of dual-cycle ergometers. So someone had to go first and someone had to go second after the start of PB. The ergometry required 10 min to complete, and there was about a five-min transition to get one subject off the ergometer and a second subject on the ergometer and ready to start their exercise prescription. We evaluated if the order of ergometry, only separated by at most 15 min, was an important consideration for the DCS and VGE outcomes.

Tables 14 and 15 show the DCS and VGE results for 27 subjects that did ergometry first and 27 subjects that did ergometry second. These results are from Phases I and II; no other tests provided the opportunity to study an order-effect for dual-cycle ergometry. Table 14 lists several physical characteristics for the 13 subjects that had VGE compared to 14 subjects without VGE in those that went first with ergometry exercise. There was no statistical difference in age, weight, height, gender distribution, or BMI between these groups. Notice that the mean latency time to the first detection of VGE was 53.5 ± 31.6 min. Compare these results with the same variables in Table 15 where 27 subjects went second with ergometry exercise. It is notable that the VGE latency time in this group increased to 94.1 ± 54.9 min, an increase that is statistically significant at $p < 0.05$ with unpaired t-test. There was no statistical difference in the DCS incidence ($p = 0.28$ with Fishers Exact χ^2) between these groups and no difference in the VGE incidence, both with 13 of 27 subjects with VGE.

TABLE 14. Physical Characteristics and Results from Subjects that did Ergometry First

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Phase I study

age (yrs)	weight (kg)	height (m)	gender 1=male	BMI (kg / m^2)	DCS 1=yes	max VGE	VGE latency time (min)
39.7	93.0	1.78	1	29.4	0	I	123
24.7	54.4	1.69	0	19.1	0	II	33
46.3	86.2	1.85	1	25.1	1	IV	16
29.3	76.2	1.80	1	23.4	0	I	51
37.0	77.1	1.83	1	23.0	0	I	71
21.9	56.7	1.67	0	20.2	1*	I	74
27.3	63.5	1.52	0	27.3	1	III	49
23.7	76.2	1.88	1	21.6	0	III	28

Phase II study

age (yrs)	weight (kg)	height (m)	gender 1=male	BMI (kg / m^2)	DCS 1=yes	max VGE	VGE latency time (min)
20.2	79.4	1.85	1	23.1	0	II	17
22.7	86.2	1.80	1	26.5	0	I	57
23.5	54.4	1.65	0	20.0	0	III	48
29.3	68.8	1.83	1	20.6	0	I	98
40.1	106.8	1.91	1	29.3	0	III	30

==

	age	weight	height	gender	BMI			VGE latency
mean	29.7	75.3	1.77	70% male	23.7			53.5
SD	8.4	15.7	0.11		3.5			31.6

==

Information from 14 that did not have VGE

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	age	weight	height	gender	BMI	DCS	max	VGE latency
mean	27.6	75.0	1.77	71% male	23.7	0	0	n / a
SD	6.7	12.8	0.08		2.3			

==

* DCS reported after the altitude exposure

TABLE 15. Physical Characteristics and Results from Subjects that did Ergometry Second

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Phase I study

age (yrs)	weight (kg)	height (m)	gender 1=male	BMI (kg / m^2)	DCS 1=yes	max VGE	VGE latency time (min)
29.0	68.0	1.70	1	23.5	0	I	118
24.7	68.0	1.85	1	19.8	0	I	94
23.3	68.0	1.63	0	25.7	1*	III	75
26.6	77.1	1.75	0	25.1	0	I	81
59.3	48.1	1.48	0	21.8	0	II	83
35.9	83.0	1.80	1	25.5	0	I	186
21.9	95.2	1.93	1	25.6	0	I	59
28.8	83.9	1.90	1	23.1	0	I	47

Phase II study

age (yrs)	weight (kg)	height (m)	gender 1=male	BMI (kg / m^2)	DCS 1=yes	max VGE	VGE latency time (min)
19.0	62.6	1.70	1	21.6	0	I	187
22.4	62.6	1.73	1	21.0	0	I	164
46.5	84.8	1.82	1	25.6	0	IV	78
46.2	70.8	1.80	1	21.8	0	IV	26
39.4	79.8	1.74	1	26.4	0	IV	26

==

	age	weight	height	gender	BMI			VGE latency
mean	32.5	73.2	1.76	77% male	23.6			94.1
SD	12.1	12.3	0.12		2.2			54.9

==

Information from 14 that did not have VGE

	age	weight	height	gender	BMI	DCS	max VGE	VGE latency
mean	32.1	78.3	1.74	78% male	25.7	0	0	n / a
SD	13.2	17.5	0.08		4.4			

==

* DCS reported after the altitude exposure
Two cases with VGE latency times of 162 and 163 min were removed from the analysis because PB time inadvertently extended.

Figure 11 shows the cumulative VGE cases plotted against VGE latency times from Tables 14 and 15. We conclude that those who went first on the ergometers showed earlier VGE latency times compared to those who went second. There were no differences in the DCS or VGE incidence observed between the two groups. The differences in latency times cannot be attributed to the fact that these data are combined from two PB studies, Phase I and Phase II. Eight of the 13 subjects (61%) did ergometry first and did the Phase I study and eight of the 13 subjects (61%) did ergometry second and did the Phase I study.
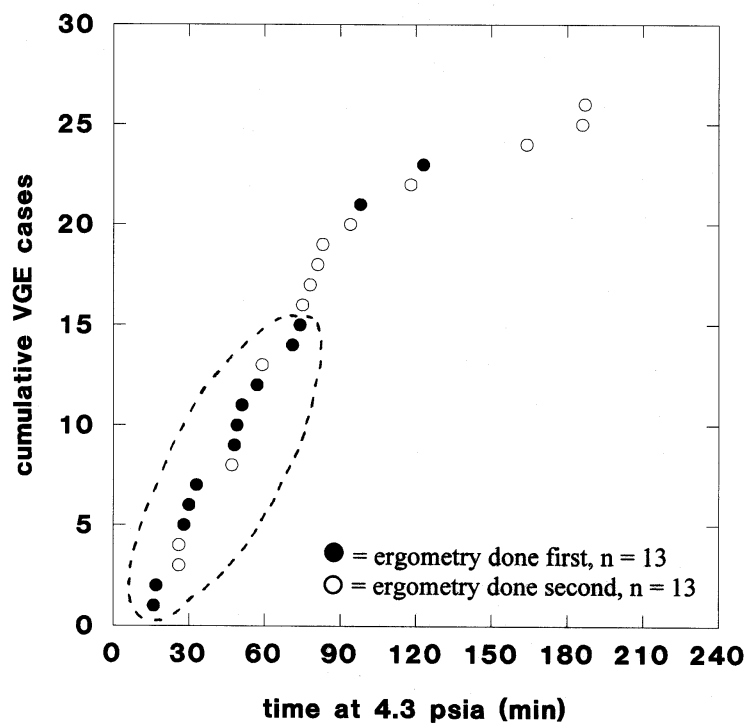
Figure 11. VGE latency time is shorter when ergometry is done at the start of exercise PB rather than 10 to 15 minutes later. Filled circles show the latency time for the first detected VGE in 13 of 27 subjects that did dual-cycle ergometry first. Open circles show the latency times for the 13 of 27 subjects that did the ergometry second. The mean latency time was 53 ± 31 min in those that went first and 94 ± 55 min in those that went second ($p < 0.05$ from unpaired t-test).

Table 16 provides additional details about the VGE by comparing the number of VGE grades between those subjects that went first to those that went second on ergometry exercise. There is no difference due to the order of ergometry in the counts of Grade I VGE. However, if ergometry is done first you have more Grade 0 counts, more Grade II counts, but fewer Grade III and IV counts. If VGE grades are combined into low (Grade I + II) and high (Grade III + IV) categories (bottom of Table 16), then the order of ergometry does not matter for low grade (p = 0.44), but going first on the ergometer means you have fewer counts of high VGE (p < 0.05). If the goal is to avoid large numbers of Grade III and IV VGE and to have more cases where no VGE are detected (Grade 0 VGE), then it is best not to delay the start of ergometry during the PB even if an early start reduces the latency time to the first VGE.

TABLE 16. Counts of VGE Grades when Ergometry is done First or Second

VGE GRADE	ERGO. FST RESULTS	(counts / total)	ERGO. SCD RESULTS	(counts / total)	p-value*
SEPARATE VGE CATEGORIES					
0	74.2%	(507 / 683)	61.4%	(341 / 555)	<0.05
I	13.7%	(94 / 683)	15.1%	(84 / 555)	0.54
II	7.6%	(52 / 683)	4.3%	(24 / 555)	0.022
III	2.8%	(19 / 683)	12.4%	(69 / 555)	<0.05
IV	1.6%	(11 / 683)	6.6%	(37 / 555)	<0.05
COMBINED VGE CATEGORIES					
I + II	21.3%	(146 / 683)	19.4%	(108 / 555)	0.54
III + IV	4.4%	(30 / 683)	19.1%	(106 / 555)	<0.05

* p-values from χ^2 test with number of VGE grades recorded compared to total VGE measurements across the two experimental conditions.

Finally, Fig. 12 shows the results of an analysis similar to that done for Fig. 10. The incidence of VGE is shown as a function of elapsed time at 4.3 psia, and epochs were converted into min. The solid curve is the best fit to VGE incidence data for those that went first on the dual-cycle ergometer, and the dashed curve are for those that went second. The best-fit solid (ergometry first) and dashed (ergometry second) curves come from a maximum likelihood optimization of a function that combines a recovery function and a response function: incidence of VGE = $[\exp^{-kt} * (t^a / (t^a + b^a))]$, where "t" is the elapsed time at altitude, the incidence of VGE are from the observed dichotomous outcomes, and k, a, and b are the fitted constants. The values of the constants to produce the solid curve are: k = 0.01027, a = 1.71, and b = 100.7, and for the dashed curve are: k = 0.00714, a = 2.138, and b = 119.1. The shifted pattern to the right is attributed to the later onset of VGE in the group that did ergometry second, but the shapes of the curves are similar.
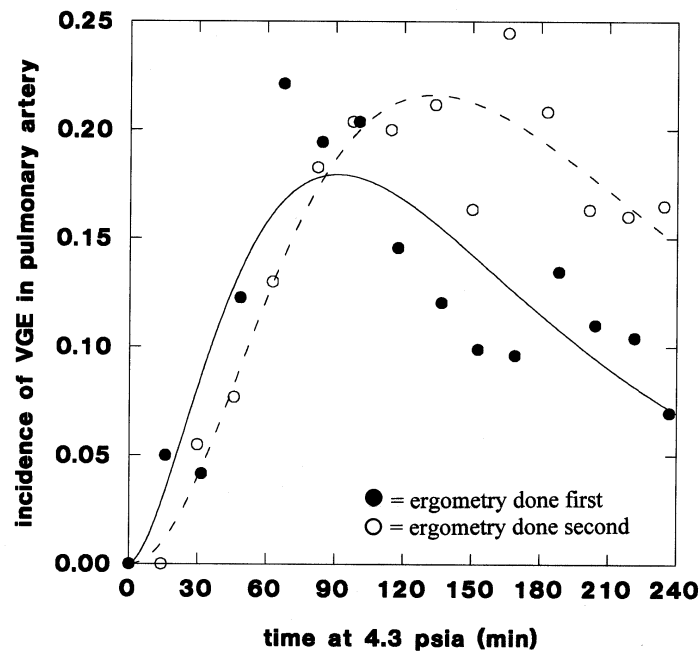
Figure 12. Incidence of VGE versus time at 4.3 psia and order of ergometry. Once VGE are first detected in the pulmonary artery there is usually a short lag phase, a rapid response phase, and a gradual recovery phase in the incidence of VGE through time. Filled circles show the incidence of VGE during 14 measurement opportunities in the 27 subjects that did the ergometry first. Open circles are the results for the 27 that did the ergometry second.

Discussion

Aerobic Fitness and Susceptibility to Hypobaric Decompression Sickness:

The central theme of this report and in this analysis is that aerobic fitness is an important consideration in a model that accounts for exercise during PB as a means to reduce the risk of DCS. Exercise is a powerful stimulus to increase tissue blood flow (2). A fit person, or even animal, is expected to mobilize the cardiopulmonary system to a greater degree than an unfit person (7,9,10,40,61,62). If fitness were not a significant consideration, then the NM and RM would not have performed well. It must be understood that the NM and RM are statistical models. The data files and models were structured to provide for the simplest treatment of the data and models to maximize the correlative relationship between VO_2 pk and DCS outcome. All exercise and even rest intervals were characterized as a percentage of VO_2 pk to apply one methodology, even when the exercise consisted of absolute work.

An example is helpful to demonstrate how the model works when DCS risk for absolute work during the PB is computed. Say that 6.0 $mL*kg^{-1}*min^{-1}$ O_2 consumption is assigned to a 70 kg and 80 kg person and each performs a two hr PB. The 70 kg person will consume 50.4 liters of O_2 compared to 57.6 liters for the 80 kg person over the two hrs, but each consume the same O_2 on a per kg per min basis. This O_2 consumption represents 14.3% of VO_2 pk based on a sample of subjects with a mean VO_2 pk of 42 $mL*kg^{-1}*min^{-1}$ (6 / 42 = 14.3%). In this example, the lighter person is fitter at 60 $mL*kg^{-1}*min^{-1}VO_2$ pk compared to the heavier person at 40 $mL*kg^{-1}*min^{-1}VO_2$ pk. If all that is know is that both consumed 6.0 $mL*kg^{-1}*min^{-1}$based on some absolute work, then the optimized model will compute the same P(DCS) for each person since it assigns a particular optimized half-time to a particular $mL*kg^{-1}*min^{-1}$. But if the fitness of the subject is also known, then a better estimate of risk for each person is available since fitness is factored into the estimate of P(DCS). The fit subject is "rewarded" in a statistical sense by having absolute work indexed upward since the absolute work is referenced to VO_2 pk. In this case, the fit person is assigned 8.5 $mL*kg^{-1}*min^{-1}$ while the unfit person is

assigned 5.7 mL∗kg^{-1}∗min^{-1}. These are not true values for O_2 consumption, but do distinguish one person from the other by accounting for aerobic fitness. In this case, the fit person has less DCS risk than the unfit person, thus using the correlative information about DCS risk and aerobic fitness even though each person did an interval of absolute work during the PB.

Another point to make is that the benefit of exercise during PB is more than just total O_2 consumption during the PB. There is also a component of how one consumes the O_2 with exercise. It appears that intense, short duration exercise followed by intermittent light exercise for a given O_2 consumption is more effective to reduce the risk of DCS than less intense intermittent exercise spaced over a longer period that still results in the same O_2 consumption. This is seen in both the data and in the ETR models since the models reflect the trends in the data. For example, Table 9 shows the estimated O_2 consumption for Phase II was 88 liter compared to 92 liters in Phase V-3. Even with slightly less computed O_2 consumption the protocol with 75% VO_2 pk for a very short period at the start of the PB resulted in no cases of DCS compared to Phase V-3. Phase I did not couple the 75% VO_2 pk with light exercise and resulted in 76 liters of O_2 consumption compared to Phase IV where intermittent light activity over 56 min resulted in 67 liters O_2 consumption. Phase I had a higher observed and predicted DCS compared to Phase IV and yet more O_2 was consumed in Phase I. The point is that just consuming greater than 70 liters of O_2 during a PB, be it a long resting PB or a shorter exercise PB, to reduce the risk of DCS is not the only consideration. The way the O_2 is consumed has a role. It appears that high intensity, short duration exercise followed by intermittent low intensity exercise for the balance of the PB is most beneficial. This has the effect of dramatically reducing the half-time in the models for N_2 removal during the PB at a time when tissue N_2 pressure is high. The mobilization of metabolic control of local tissue blood flow caused by an intense bout of exercise is then maintained by intermittent low intensity exercise that facilitates the muscle pump to return venous blood to the lungs. A fit subject actually consumes more O_2 over the same period compared to an unfit subject, which ultimately translates to more blood flow per kg of metabolizing tissue per interval of time. This has the effect of keeping the half-time smaller

for faster N_2 removal in the fit person compared to the unfit person doing the same work as defined by a percentage of VO_2 pk.

Age and Gender:

Recent reports document a statistical association between physical characteristics, such as age, gender, and physical fitness, and the risk of DCS and VGE in both diving (9,10,35,63) and aviation (12,13,24,45,46,49,56) decompressions. These reports confirm some of the observations about aviator DCS during World War II (25). Both the historical and recent reports stimulated us to evaluate gender and age as explanatory variables in these data. It is important to understand if there is an association with age in our DCS and VGE data since the average age on the day of EVA in 68 astronauts over 171 EVAs since the Space Shuttle became operational is 43.4 ± 5.1 years SD. This is about 10 years older than tests subjects used in our research.

Since there are limited data available to us, and since these PRP tests were not designed *per se* to evaluate fitness, gender, or age, it is inevitable that these explanatory variables come in to and out of statistical significance in the various regressions. Gender was found to be a significant explanatory variable in the NM, but gender was not a significant predictor variable in the RM. Age was found to be a significant explanatory variable in the RM, but not in the NM. We did not evaluate these explanatory variables in the VGE data for this report, but advancing age is associated with more VGE in an evaluation of similar data (12). We conclude that it is likely the lack of sufficient data that allows gender to be only significant in the NM, and only age to be significant in the RM. We suspect that both variables would be significant predictors of DCS given additional data collected in a way to specifically test these variables.

It is easy to understand how modification of some environmental variables affects the DCS outcome. If you dive deep, stay long, and ascend quickly to the surface, then you may acquire DCS. If you do not perform a PB, ascend to 4.3 psia (30,250 feet altitude) breathing 100% O_2, and vigorously exercise the lower body, then you may acquire DCS. What is difficult to understand and to show is how exercise during PB affects outcomes and how differences in

variables that defines who we are, like age, weight, and gender affect outcomes. It is even more difficult when some variables change in a cyclical fashion, such as water retention associated with the menstrual cycle in women (45,46,56,64). There are at least three factors to consider about gender and the risk of DCS: 1) change in DCS risk within the normal menstrual cycle, 2) change in DCS risk with the use of a contraceptive, and 3) difference in DCS risk between men and women. It gets even more complicated when age is superimposed on the menstrual cycle, or if there has been a hysterectomy.

The most recent information by Webb (56) draws seemingly contrary conclusions than recent information from Lee (36). However, the analysis by Webb included both DCS (numerator) and non-DCS cases (denominator) in 269 women-exposures to different altitudes while Lee only included those 150 women that presented themselves for hyperbaric treatment (numerator) after SCUBA diving. In each study there were data on a subset of women that used contraceptives. In summary, Webb showed that the use of contraceptive was associated with a greater risk of DCS, and Lee showed for those reporting with DCS, the use of contraceptive was irrelevant. Webb showed there was no increased risk of DCS in the first half of the menstrual cycle, and Lee showed for those with DCS, there is a greater number of cases associated with the first half of the menstrual cycle. Finally, Webb showed there is an increased risk of DCS in the second half of the menstrual cycle if women use contraceptive, and Lee showed for those with DCS, there is about the same number of cases associated with the second half of the menstrual cycle whether a contraceptive was used (29 / 63 = 46%) or was not used (31 / 87 = 36%). It is not surprising that there is still no consensus of opinion on how each of these factors alone or in combination affect the risk of DCS.

Age was a variable important to describe DCS in the RM. There is good documentation to show that increasing age is associated with increased reporting of DCS. Gray (25) showed a linear increase in relative DCS susceptibility with age over an $18 - 28$ year range in men. Sulaiman et al (49) reported a three-fold increase in susceptibility between the age group $18 - 21$ years and the group greater than 42 years. This is in agreement with a three-fold increase in incidence between 19 to 25 and 40 to 45 year olds published by Heimbach and Sheffield (28), and similar to results reported by Webb et al (56). Our inability to show an association between

age and DCS in the NM may be related to the low overall decompression stress of the tests in that subset of data and our inability to recruit large numbers of older subjects.

Body composition changes with age. Finch (19) described age-related changes in several body systems. There is an increase in fat content and a decrease in water content such that there is a linear decline in specific gravity from 1.080 at age 20 to 1.033 at age 70 years. The connective tissue matrix changes with age; collagen becomes more stable (less flexible), and the basal lamina becomes thicker. Cardiac output reduces about one percent per year along with an increase in peripheral vascular resistance. An aging lung may reduce the ability of the lung to filter VGE from the circulation or excrete the evolved gas to the atmosphere. The internal surface area of the lung declines linearly from about 75 m^2 at age 20 to 62 m^2 at age 70 years, vital capacity decreases with a subsequent increase in residual volume, and there is an increase in lung compliance. There is a progressive increase in the alveolar-arterial O_2 partial pressure difference with age attributed to diffusion impairment across the alveoli and by increased ventilation and perfusion mismatching.

In summary, aging favors more inert gas to be present with a reduced ability to transport the gas, dissolved or evolved, from the tissues to the lungs to the atmosphere. There is a steady decline in physical fitness with age. A decline in fitness rather than age *per se* may be more closely related to an increased risk of DCS and VGE, but the two are often linked (9,10,56). Some divers and aviators do "age better than others", so it is not justified to characterize all older men and women as being at a greater risk of DCS and VGE.

Application of Models: An Example

Our application of these models is to prevent DCS in astronauts. The tests were conducted under conditions similar to what would actually be implemented by NASA if the test had a favorable outcome, i.e., $\leq$ 15% total DCS and $\leq$ 20% Grade IV VGE, both with 95% confidence. The tests were conducted with several important variables held constant, such as adynamia before and during the altitude exposure, the length of time at 4.3 psia, and the type and intensity of exercise done at 4.3 psia. In effect, variations of the exercise during the PB and the

length of the total PB were the only conditions that changed from one test to another if we assume our samples of subjects were comparable. The subjects did provide a narrow range for age, gender distribution, and aerobic fitness, but were otherwise homogeneous in height, weight, BMI, percentage of body fat, etc., due to our subject inclusion criteria. At best, the RM and NM would predict the same DCS outcome as observed given the same input conditions from the tests (see comparisons in Tables 11 and 13).

The further we deviate from the range of conditions from the tests the less confident we become in the predicted outcome when we apply the models to a simulated PB. It is preferable to interpolate within the range of experience in our tests rather than extrapolate to untested conditions, i.e., very short or very long total PB times, or exotic combinations of relative or absolute work during the PB. For example, there is no provision in these models to account for any other condition than adynamic. Adynamia is our analog of μ-gravity adaptation (23,42,51).

With the above preface, an example is provided to show the application of the NM and RM to a simulated 4-hr EVA from the proposed Crew Excursion Vehicle (CEV) during a trip to the moon; a simulation that is an extrapolation from the models since total PB time is short at 90 min, the crew live at 10.5 psia prior to the EVA, and the proposed exercise during the PB deviates from what was tested. In this example, the astronaut is a 43 yo male with a VO_2 pk of 50 $mL*kg^{-1}*min^{-1}$. He has been breathing a ppN_2 of 8.0 psia and a ppO_2 of 2.5 psia for several days. Therefore, the CEV environment provides a total pressure of 10.5 psia with 23.8% O_2 (2.5 / 10.5). The suit pressure is 4.3 psia, so the TR at the start of EVA is 1.86 (8.0 / 4.3) if no PB is performed. The NM predicts 6.1% DCS while the RM model predicts 8.6% DCS under these conditions, but PB associated with suit donning and slow depressurization to 4.3 psia would provide some protection from DCS. It is judged that this risk is unacceptable given the lack of hyperbaric treatment capability in the CEV. So an exercise PB option is planned.

Table 17 lists the details of the PB. The astronaut will exercise using dual-cycle ergometry at 50% of his VO_2 pk for 20 min while breathing O_2 from a mask. He continues to breathe from the mask an additional 20 min as he dons the Liquid Cooling and Ventilation Garment, and is active during this time at 20% VO_2 pk. He will then remove the mask and be

re-exposed to a ppN$_2$ of 8.0 psia in the CEV during a 20 min suit donning procedure. It is estimated that he will also work at 20% of VO$_2$ pk during this activity. Suit purge, leak check, and other final checks plus final ascent to 4.3 psia will take 30 min with the astronaut in a rested state, at 9.5% VO$_2$ pk.

TABLE 17: Example Application of Exercise Prebreathe Models

PB	1	2	3	4	5	6
activity	W	R	T	A	A	Q
%VO$_2$	25.0	50.0	25.0	20.0	20.0	9.5
ml/kg/min	12.5	25.0	12.5	10.0	10.0	4.7
time	3	17	3	17	20	30
P$_a$	0	0	0	0	8.0	0

R = relative work (dual-cycle ergometry)
A = absolute work (crank-and-yank devices)
Q = quiet (rest) periods
T = transition from high intensity, low duration exercise to low intensity, long duration exercise, or transition from relative work to rest
W = warm up work (ramping up to dual-cycle relative work)

The information in Table 17 is evaluated by the computer using Eq. 4 with the optimized coefficients for λ_2 for both the NM ($\lambda_2 = 0.030$) and the RM ($\lambda_2 = 0.025$). The computed final tissue ppN2 is 6.62 psia for the NM and 6.69 psia for the RM. This is a decrease over 90 min from the initial equilibrium tissue ppN2 of 8.0 psia. Therefore, the computed ETR for the NM is 1.54 (6.62 / 4.3) and 1.55 (6.69 / 4.3) for the RM. The ETR for the NM plus the information about gender (sex = 1) are evaluated in Eq. 14. The P(DCS) for the NM is 0.001 (0.1%). The ETR for the RM plus the information about age (43 yo) are evaluated in Eq. 15. The P(DCS) for the RM is also 0.001 (0.1%).

$$P(DCS) \text{ from NM} = \frac{\exp(-25.56 + 12.83 * ETR - 1.037 * SEX)}{(1 + \exp(-25.56 + 12.83 * ETR - 1.037 * SEX))} \qquad \text{Eq. 14}$$

$$P(DCS) \text{ from } RM = \frac{\exp(-31.71 + 14.55 * ETR + 0.053 * AGE)}{(1 + \exp(-31.71 + 14.55 * ETR + 0.053 * AGE))} \qquad \text{Eq. 15}$$

These estimates of DCS risk are similar, are much less than the risk without the exercise PB intervention, and are deemed acceptable in relation to the importance of the EVA from the CEV on the way to the moon.

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Appendices

Exercise Prebreathe Details for Phase I through V-3 and Exercise at 4.3 psia

Appendix   **page**

Appendix A: Maximal Aerobic Capacity Test using Dual-Cycle Ergometry

The subject was instrumented for EKG, heart rate, and O_2 consumption and seated on the leg ergometer. The subject began pedaling both the Monarch 818E leg ergometer and the Monarch 881 arm ergometer, with a low workload, at a cadence of 65 rpm to become familiar with maintaining equal cadence for both ergometers. Thereafter, the test began at workloads described in the tables below for males and females. The workloads on the ergometer were controlled manually. The workloads on both ergometers were increased at 2.5 mins into each exercise level. The subject was instructed to pedal as long as possible while still maintaining a cadence of 65 rpms on both ergometers. At two min of each stage, heart rate, and O_2 consumption values were recorded. The mean O_2 consumption for each exercise stage was determined to be the average of the values collected in the last min of each stage. The test was terminated when the subject reached volitional fatigue or could not maintain the required arm or leg cadence. VO_2 pk and pk heart rates were accepted as the highest O_2 consumption and heart rates over a 60 sec period, which typically occurred in the last stage of the maximal exercise sessions.

Oxygen consumption versus heart rate and O_2 consumption versus workload of the maximal exercise tests were plotted using the values recorded at each stage. Examples of these are shown below. A linear regression was determined for each exercise graph, and the slope and y-intercept of the lines describing these relationships were used to determine the total workloads and predict the heart rates for each stage of the 75% submaximal exercise sessions. Of the total workload prescribed for submaximal exercise, 88% was performed by the legs and 12% was performed by the arms.

Appendix B: Maximal Aerobic Capacity Test Protocol for Male and Female

MALE

Stage	Time (min.)	Leg Load (W) 65 rpm	Arm Load (W) 65 rpm	Total Workload (W)
1	0-2.5	75	11.3	86.3
2	2.5-5.0	125	18.7	143.7
3	5.0-7.5	175	26.3	201.3
4	7.5-10.0	225	33.7	258.7
5	10.0-12.5	275	41.3	316.3
6	12.5-15.0	325	48.7	373.7
7	15.0-17.5	375	56.3	431.3

FEMALE

Stage	Time (min.)	Leg Load (W) 65 rpm	Arm Load (W) 65 rpm	Total Workload (W)
1	0-2.5	53	7.9	60.9
2	2.5-5.0	88	13.1	101.1
3	5.0-7.5	123	18.4	141.4
4	7.5-10.0	158	23.6	181.6
5	10.0-12.5	193	28.9	221.9
6	12.5-15.0	228	34.1	262.1
7	15.0-17.5	263	39.4	302.4

$y = 0.025x - 1.709 \quad r^2 = 0.929$

$y = 0.008x + 0.946 \quad r^2 = 0.856$
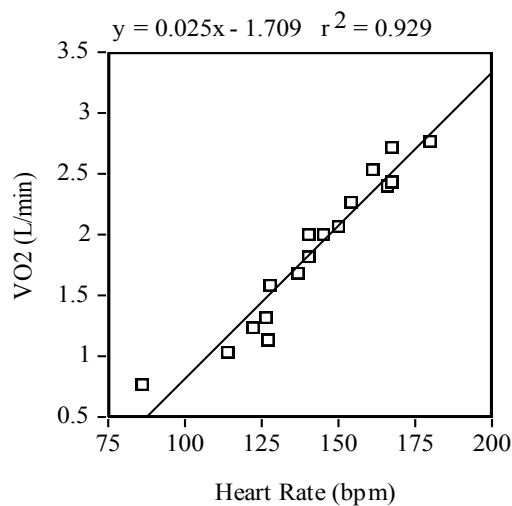
Figure 1: Heart Rate vs. Oxygen Consumption
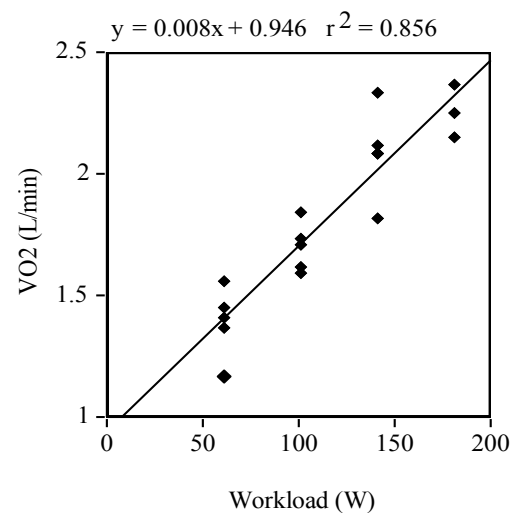
Figure 2: Workload vs. Oxygen Consumption

Appendix C: Execution of 75% VO$_2$ pk Protocol

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event	Δt (min)	total time (min)	% of VO$_2$ pk
increment stage 1	1	1	37.5%
increment stage 2	1	2	50.0%
increment stage 3	1	3	62.5%
exercise stage	7	10	75.0%

===

Research Protocol: Both arm and leg ergometry was done, so the total workload expressed as watts at 75% of VO$_2$ pk from a linear regression had to be partitioned into arm watts and leg watts. We used 88% of prescribed watts for the legs and 12% of prescribed watts for the arms for the three 1-min warm up stages and the 7-min exercise stage.

Operational Protocol: Leg ergometry was performed and surgical tubing was used in place of an arm ergometer. We used 88% of the prescribed watts for the legs and the balance of 12% of the total workload was attributed to upper body work with the surgical tubing for the arms for the three 1-min warm up stages and the 7-min exercise stage.

Appendix D: Time and Events for Phase I through IV

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Phase	I	II	III	IV
Number of Subjects	**47**	**45**	**9**	**56**

===

start adynamia in recumbent subjects	-100	-100	-100	-100 (min)
start prebreathe and dual-cycle ergo. in Phase I and II	0	0	0	0
start 56 min of EVA prep. Exercise	--	--	--	4
end dual-cycle ergometry	10	10	--	--
start chamber depress from 14.7 psi to 9.6 psia in 20 min, then to 10.2 psi in 10 min	50	50	50	50
start 24 min of EVA prep. exercise	--	55	55	--
switch from 100% O_2 to 26.5% O_2	80	80	80	80
stop EVA prep. exercise	95	95	95	95
switch from 26.5% O_2 to 100% O_2 and repress chamber from 10.2 psi to 14.7 psi in 5 min	110	110	110	110
continue resting prebreathe	115	115	115	115
start chamber depress from 14.7 psi to 4.3 psi in 30 min	150	150	150	150
start 240 min of simulated EVA exercise	180	180	180	180
end test	420	420	420	420

===

Appendix E: Phase I Exercise Details

Pull Station (PS)
pull with both arms to: pounds of pull $= 0.25 * $ body weight (lbs) $+ 25$

hold 10 seconds and rest for 5 seconds
repeat contraction -- 16 cycles

Torque Station (TSLH)
pull and hold with left hand for 5 seconds at 25 ft-pounds at the next 5 second cadence
push and hold with the left for 5 seconds at 25 ft-pounds at the next 5 second cadence
do for two mins on one stud then shift to another
repeat contractions -- 20 - 24 cycles depending on how much time it takes to move torque wrench from one stud to the next

Torque Station (TSRH)
pull and hold with the right hand for 5 seconds at 25 ft-pounds at the next 5 second cadence
push and hold with the right hand for 5 seconds at 25 ft-pounds at the next 5 second cadence
do for two mins on one stud then shift to another
repeat contractions -- 20 - 24 cycles depending on how much time it takes to move torque wrench from one stud to the next

Arm Station (AS1)
make 5 sit-ups in a 5 second against the resistance of the bungee while holding torque fixture with both hands
5 contractions of the right arm in 5 seconds against the bungee
5 contractions of the left arm in 5 seconds against the bungee
rest 5 seconds
repeat contractions -- 12 cycles

Arm Station (AS2)
make 4 sit-ups in a 5 second against the resistance of the bungee while holding torque fixture with both hands
rest 5 seconds
4 contractions of the right arm in 5 seconds against the bungee
4 contractions of the left arm in 5 seconds against the bungee
rest 5 seconds
repeat contractions -- 12 cycles

Hand Station (HS)
two min with right hand and two min with left
one right hand contraction and hold for the 5 second interval
rest 10 seconds

repeat right hand contraction for two mins -- 8 cycles with right hand
one left hand contraction and hold for the 5 second interval
rest 10 seconds
repeat left hand contraction for two mins -- 8 cycles with left hand

Rest Station (VGE)
four min duration to relax hands, VGE monitoring, and symptom report

Appendix F: Phase I Exercise Profile

START TIME	SUB1	SUB2	DOP TECH
0	AS1	AS1	REST
4	AS1	AS1	REST
8	VGE	HS	DOP1
12	PS	VGE	DOP2
16	TSRH	PS	DOPDT
20	AS2	TSRH	REST
24	VGE	AS2	DOP1
28	PS	VGE	DOP2
32	TSLH	PS	DOPDT
36	HS	TSLH	REST
40	VGE	HS	DOP1
44	PS	VGE	DOP2
48	TSRH	PS	DOPDT
52	AS2	TSRH	REST
56	VGE	AS2	DOP1
60	REST	REST	REST
64	PS	VGE	DOP2
68	TSLH	PS	DOPDT
72	HS	TSLH	REST
76	VGE	HS	DOP1
80	PS	VGE	DOP2
84	TSRH	PS	DOPDT
88	AS2	TSRH	REST
92	VGE	AS2	DOP1
96	PS	VGE	DOP2
100	TSLH	PS	DOPDT
104	HS	TSLH	REST
108	VGE	HS	DOP1
112	PS	VGE	DOP2
116	TSRH	PS	DOPDT
120	REST	REST	REST
124	AS2	TSRH	REST
128	VGE	AS2	DOP1
132	PS	VGE	DOP2
136	TSLH	PS	DOPDT
140	HS	TSLH	REST
144	VGE	HS	DOP1
148	PS	VGE	DOP2
152	TSRH	PS	DOPDT
156	AS2	TSRH	REST

160	VGE	AS2	DOP1
164	PS	VGE	DOP2
168	TSLH	PS	DOPDT
172	HS	TSLH	REST
176	VGE	HS	DOP1
180	REST	REST	REST
184	PS	VGE	DOP2
188	TSRH	PS	DOPDT
192	AS2	TSRH	REST
196	VGE	AS2	DOP1
200	PS	VGE	DOP2
204	TSLH	PS	DOPDT
208	HS	TSLH	REST
212	VGE	HS	DOP1
216	PS	VGE	DOP2
220	TSRH	PS	DOPDT
224	AS2	TSRH	REST
228	VGE	AS2	DOP1
232	PS	VGE	DOP2
236	TSLH	PS	DOPDT
240	END	END	END

Appendix G: Time and Events for Phase II

Elapsed Time from start of dual cycle ergometry on 100% O_2

-120   1. Start Doppler Technician (DT) prebreathe at 7:30 a.m. for the 4.5 hr
prebreathe option.

-100   2. Start period of adynamia at 7:50 a.m. Subjects are recumbent and breathe air for 100
mins prior to start of dual cycle exercise.

----

0   3. Start dual cycle exercise at 9:30 a.m. with all subjects on 100% O_2, two at Hermann
and three at Duke.

50   4. At 10:20 a.m. the dual cycle exercise is over. Depress the chamber from site pressure
to 9.6 psia in 20 mins and maintain the subjects and DT on 100% O_2 for an additional 10
mins as you repress to 10.2 psia.

55   5. Start warm-up for EVA Prep activity. Do TSRH.

59   6. Continue warm-up for EVA Prep activity. Do TSLH.

63   7. Rest in preparation for AS2 activity.

67   8. Do AS2 activity.

71   9. Rest in preparation for AS2 activity.

75   10. Do AS2 activity.

79   11. Rest in preparation for AS2 activity.

80   12. At 10:50 a.m. switch to bottled gas supply and breathe the 26.5% O_2 -
73.5% N_2 mixture for 30 mins. DT stays on 100% O_2. Continue EVA Prep exercises
for 12 more mins.

83   13. Do AS2 activity.

87   14. Rest in preparation for AS2 activity.

91   15. Do AS2 activity.

95   16. At 11:05 a.m., discontinue EVA Prep activities.

110   17. At 11:20 a.m. switch from mixed gas supply to 100% O_2, then repress the chamber
to 14.7 psia (site pressure) in 5 mins.

115   18. At 11:25 a.m. continue a 35 min prebreathe on 100% O_2 at site pressure.

150   19. At 12:00 a.m. the subjects have completed 250 mins of adynamia prior to depress to
4.3 psia, 120 mins of 100% O_2 prebreathing, and 30 mins of breathing 26.5% O_2. The
DT has completed 4.5 hrs of uninterrupted 100% O_2 prebreathing. At 12:00 a.m. depress
chamber to 4.3 psia in 30 mins.

180   20. At 12:30 a.m. begin four hrs of exercise that simulates EVA activity and
monitor for VGE and DCS signs and symptoms. It is a nine hr day for the DT
and a 8.7 hr day for the subjects.

Appendix H: Time and Events for Phase III

Elapsed Time from start of prebreathe on 100% O_2

-120   1. Start Doppler Technician (DT) prebreathe at 7:30 a.m. for the 4.5 hr
          prebreathe option.

-100   2. Start period of adynamia at 7:50 a.m. Subjects are recumbent and breathe air for 100
          mins prior to start of prebreathe.

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0   3. Start prebreathe at 9:30 a.m. with all subjects on 100% O_2, two at Hermann and three
          at Duke.

50   4. At 10:20 a.m. start the depress the chamber from site pressure to 9.6 psia in
          20 mins and maintain the subjects and DT on 100% O_2 for an additional 10 mins as you
          repress to 10.2 psia.

55   5. Start warm-up for EVA Prep activity. Do TSRH.

59   6. Continue warm-up for EVA Prep activity. Do TSLH.

63   7. Rest in preparation for AS2 activity.

67   8. Do AS2 activity.

71   9. Rest in preparation for AS2 activity.

75   10. Do AS2 activity.

79   11. Rest in preparation for AS2 activity.

80   12. At 10:50 a.m. switch to bottled gas supply and breathe the 26.5% O_2 -
          73.5% N_2 mixture for 30 mins. DT stays on 100% O_2. Continue EVA Prep exercises
          for 12 more mins.

83   13. Do AS2 activity.

87   14. Rest in preparation for AS2 activity.

91   15. Do AS2 activity.

95   16. At 11:05 a.m., discontinue EVA Prep activities.

110   17. At 11:20 a.m. switch from mixed gas supply to 100% O_2, then repress the chamber
          to 14.7 psia (site pressure) in 5 mins.

115   18. At 11:25 a.m. continue a 35 min prebreathe on 100% O_2 at site pressure.

150   19. At 12:00 a.m. the subjects have completed 250 mins of adynamia prior to depress to
          4.3 psia, 120 mins of 100% O_2 prebreathing, and 30 mins of breathing 26.5% O_2. The
          DT has completed 4.5 hrs of uninterrupted 100% O_2 prebreathing. At 12:00 a.m. depress
          chamber to 4.3 psia in 30 mins.

180   20. At 12:30 a.m. begin four hrs of exercise that simulates EVA activity and monitor for
          VGE and DCS signs and symptoms. It is a nine hr day for the DT and a 8.7 hr day for
          the subjects.

Appendix I: Prebreathe Exercise Protocol for Phase IV

Elapsed time (min)	event
0	rest
4	do TSRH
8	do TSLH
12	do AS2
16	rest
20	do TSRH
24	do TSLH
28	do AS2
32	rest
36	do AS2
40	rest
44	do AS2
48	rest (7 min of rest as depress to 9.6 psia is done)
55	do TSRH
59	do TSLH
63	rest
67	do AS2
71	rest
75	do AS2
79	rest
83	do AS2
87	rest
91	do AS2
95	stop activity

Appendix J: Phase II, III, IV, V-1 through V-3 Exercise Details

Pull Station / Arm Station (PS/AS2)
pull with both arms to: pounds of pull $= 0.25 * $ body weight (lbs) $+ 25$

hold 30 seconds and rest for 30 seconds
make 4 sit-ups in a 5 second against the resistance of the bungee while holding torque
fixture with both hands
rest 5 seconds
4 contractions of the right arm in 5 seconds against the bungee
4 contractions of the left arm in 5 seconds against the bungee
rest 5 seconds
repeat contractions -- 9 cycles

Torque Station (TSLH)
pull and hold with left hand for 5 seconds at 25 ft-pounds at the next 5 second cadence
push and hold with the left for 5 seconds at 25 ft-pounds at the next 5 second cadence
do for two mins on one stud then shift to another
repeat contractions -- 20 - 24 cycles depending on how much time it takes to move torque
wrench from one stud to the next

Torque Station (TSRH)
pull and hold with the right hand for 5 seconds at 25 ft-pounds at the next 5 second
cadence
push and hold with the right hand for 5 seconds at 25 ft-pounds at the next 5 second
cadence
do for two mins on one stud then shift to another
repeat contractions -- 20 - 24 cycles depending on how much time it takes to move torque
wrench from one stud to the next

Arm Station (AS1)
make 5 sit-ups in a 5 second against the resistance of the bungee while holding torque
fixture with both hands
5 contractions of the right arm in 5 seconds against the bungee
5 contractions of the left arm in 5 seconds against the bungee
rest 5 seconds
repeat contractions -- 12 cycles

Arm Station (AS2)
make 4 sit-ups in a 5 second against the resistance of the bungee while holding torque
fixture with both hands
rest 5 seconds
4 contractions of the right arm in 5 seconds against the bungee
4 contractions of the left arm in 5 seconds against the bungee
rest 5 seconds
repeat contractions -- 12 cycles

Hand Station (HS)
two min with right hand and two min with left
one right hand contraction and hold for the 5 second interval
rest 10 seconds
repeat right hand contraction for two mins -- 8 cycles with right hand
one left hand contraction and hold for the 5 second interval
rest 10 seconds
repeat left hand contraction for two mins -- 8 cycles with left hand

Rest Station (VGE)
four min duration to relax hands, VGE monitoring, and symptom report

Appendix K: Phase II, III, IV, V-1 through V-3 Exercise Profile

START TIME	SUB1	SUB2	DOP TECH
0	AS1	AS1	REST
4	AS1	AS1	REST
8	VGE	HS	DOP1
12	HS	VGE	DOP2
16	TSRH	HS	DOPDT
20	PS/AS2	TSRH	REST
24	VGE	PS/AS2	DOP1
28	PS/AS2	VGE	DOP2
32	TSLH	PS/AS2	DOPDT
36	HS	TSLH	REST
40	VGE	HS	DOP1
44	PS/AS2	VGE	DOP2
48	TSRH	PS/AS2	DOPDT
52	PS/AS2	TSRH	REST
56	VGE	PS/AS2	DOP1
60	REST	REST	REST
64	PS/AS2	VGE	DOP2
68	TSLH	PS/AS2	DOPDT
72	HS	TSLH	REST
76	VGE	HS	DOP1
80	PS/AS2	VGE	DOP2
84	TSRH	PS/AS2	DOPDT
88	PS/AS2	TSRH	REST
92	VGE	PS/AS2	DOP1
96	PS/AS2	VGE	DOP2
100	TSLH	PS/AS2	DOPDT
104	HS	TSLH	REST
108	VGE	HS	DOP1
112	PS/AS2	VGE	DOP2
116	TSRH	PS/AS2	DOPDT
120	REST	REST	REST
124	PS/AS2	TSRH	REST
128	VGE	PS/AS2	DOP1
132	PS/AS2	VGE	DOP2
136	TSLH	PS/AS2	DOPDT
140	HS	TSLH	REST
144	VGE	HS	DOP1
148	PS/AS2	VGE	DOP2
152	TSRH	PS/AS2	DOPDT
156	PS/AS2	TSRH	REST

160	VGE	PS/AS2	DOP1
164	PS/AS2	VGE	DOP2
168	TSLH	PS/AS2	DOPDT
172	HS	TSLH	REST
176	VGE	HS	DOP1
180	REST	REST	REST
184	PS/AS2	VGE	DOP2
188	TSRH	PS/AS2	DOPDT
192	PS/AS2	TSRH	REST
196	VGE	PS/AS2	DOP1
200	PS/AS2	VGE	DOP2
204	TSLH	PS/AS2	DOPDT
208	HS	TSLH	REST
212	VGE	HS	DOP1
216	PS/AS2	VGE	DOP2
220	TSRH	PS/AS2	DOPDT
224	PS/AS2	TSRH	REST
228	VGE	PS/AS2	DOP1
232	PS/AS2	VGE	DOP2
236	TSLH	PS/AS2	DOPDT
240	END	END	END

Appendix L: Prebreathe Exercise Protocol for PhaseV-1, V-2, and V-3

V-1: two min exercise with two min rest in a 90 min total prebreathe, with arms and legs moving for the two min. Note: middle of exercise has a 6 min period of rest.
160 min adynamia before start of prebreathe, with adynamia maintained during the 90 min prebreathe, 30 min ascent and 240 min during the exposure to 4.3 psia

2 min rest at start of PB
2 min at 40% VO2 pk
2 min rest
2 min at 50% VO2 pk
2 min rest
2 min at 60% VO2 pk
2 min rest
2 min at 60% VO2 pk
2 min rest
2 min at 60% VO2 pk
6 min rest
2 min at 60% VO2 pk
2 min rest
2 min at 60% VO2 pk
2 min rest
2 min at 60% VO2 pk
2 min rest
2 min at 60% VO2 pk
2 min rest
2 min at 50% VO2 pk
46 min rest
30 min ascent
240 min at 4.3 psia

V-2: three min exercise with two min rest in a 90 min total prebreathe. After two min of upper and lower body exercise, the arms are stopped, but the legs continue for the third min. Note: my records show we did not start Protocol 2 with the initial two min rest. Note: middle of exercise has a 4 min rest.
160 min adynamia before start of prebreathe, with adynamia maintained during the 90 min prebreathe, 30 min ascent and 240 min during the exposure to 4.3 psia

2 min at 50% VO2 pk
2 min rest
3 min at 60% VO2 pk
2 min rest
3 min at 60% VO2 pk
2 min rest
3 min at 60% VO2 pk
4 min rest

3 min at 60% VO2 pk
2 min rest
3 min at 60% VO2 pk
2 min rest
3 min at 60% VO2 pk
46 min rest
30 min ascent
240 min at 4.3 psia

V-3: three min exercise with two min rest plus 24 min of light exercise in a 120 min total
prebreathe. After two min of upper and lower body exercise, the arms are stopped, but
the legs continue for the third min. Note: we do start Protocol 3 with the initial two min
rest. Note: middle of exercise has a 4 min rest.
160 min adynamia before start of prebreathe, with adynamia maintained during the 120
min prebreathe, 30 min ascent and 240 min during the exposure to 4.3 psia

2 min rest
2 min at 50% VO2 pk
2 min rest
3 min at 60% VO2 pk
2 min rest
3 min at 60% VO2 pk
2 min rest
3 min at 60% VO2 pk
4 min rest
3 min at 60% VO2 pk
2 min rest
3 min at 60% VO2 pk
2 min rest
3 min at 60% VO2 pk
14 min transfer from ergometer to exercise cot
4 min TSRH exercise
4 min TSLH exercise
4 min rest
4 min AS2 exercise
4 min rest
4 min AS2 exercise
4 min rest
4 min AS2 exercise
4 min rest
4 min AS2 exercise
30 min rest
30 min ascent
240 min at 4.3 psia

Appendix M: Phase V-3 Exercise During Prebreathe Details

Torque Station (TSLH)
pull and hold with left hand for 5 seconds at 25 ft-pounds at the next 5 second cadence
push and hold with the left for 5 seconds at 25 ft-pounds at the next 5 second cadence
do for two mins on one stud then shift to another
repeat contractions -- 20 - 24 cycles depending on how much time it takes to move torque
wrench from one stud to the next

Torque Station (TSRH)
pull and hold with the right hand for 5 seconds at 25 ft-pounds at the next 5 second
cadence
push and hold with the right hand for 5 seconds at 25 ft-pounds at the next 5 second
cadence
do for two mins on one stud then shift to another
repeat contractions -- 20 - 24 cycles depending on how much time it takes to move torque
wrench from one stud to the next

Arm Station (AS2)
make 4 sit-ups in a 5 second against the resistance of the bungee while holding torque
fixture with both hands
rest 5 seconds
4 contractions of the right arm in 5 seconds against the bungee
4 contractions of the left arm in 5 seconds against the bungee
rest 5 seconds
repeat contractions -- 12 cycles