Lower Body Adynamia as a Factor to Reduce the Risk of Hypobaric Decompression Sickness

JOHNNY CONKIN, PH.D., M.S., AND
MICHAEL R. POWELL, PH.D., M.S.

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Background: We define lower body adynamia (LBA) as restricted lower body movement, particularly walking, during both the denitrogenation phase at site pressure and during the exercise phase while at altitude. ***Hypothesis:*** Our null hypothesis is that subjects who are adynamic in the lower body but do upper body exercise will be at similar risk of decompression sickness (DCS) and venous gas emboli (VGE) as subjects who randomly walk but do no planned exercise while at altitude. ***Methods:*** We selected a data set that contained 1401 altitude exposures with the following conditions: a) walking was part of the exercise at altitude; or b) there was no planned exercise done at altitude but walking was not restricted; or c) LBA was inforced, but upper body exercise was done at altitude. We used logistic regression (LR) on all 1401 exposures, a log logistic survival analysis (SA) on a subset of data from "a" and "c" (n = 234), and estimated a model for how the incidence of VGE changes through time. ***Results:*** The estimated probabilities of DCS and VGE with 95% confidence intervals (CIs) from the LR with a simulation of a 3-h oxygen prebreathe, a 4-h exposure to 4.3 psia in a male, and exercise and LBA conditions as described above are:

Condition	P(DCS)	n	95%	CIs	P(VGE)	n	95%	CIs
a	0.33	876	0.27	0.40	0.69	876	0.63	0.74
b	0.21	449	0.16	0.29	0.52	215	0.43	0.61
c	0.13	76	0.07	0.24	0.32	76	0.22	0.45

Conclusion: LBA that includes upper body exercise appears to be as protective against DCS and VGE as random walking by subjects who did no prescribed exercise while at altitude, and is more protective than exercise that included walking. Our conclusions are based on an assumption that we have adequately controlled, through our data selection process and the use of multivariable models, important variables in tests that were not done at the Johnson Space Center.

Keywords: survival analysis, logistic regression, venous gas emboli, extravehicular activity, probability models, micronuclei.

WE HAVE REPORTED that walking in an altitude chamber is not a reasonable activity if the results from research on decompression sickness (DCS) are then applied to astronauts who perform extravehicular activities (EVAs) (22,23). It has been known for decades that exercise increases the risk of DCS, generally in the limb performing the exercise (7,8,15,17). While it is easy to walk for hours, it is impossible to carry one's weight in a handstand for more than a few minutes. Walking is such a natural event that it is frequently ignored as being exercise in research on DCS. In the Preface of his book, *The Origin of Humankind*, Richard Leaky wrote that the first key event in human evolution was bipedal locomotion, some seven million years ago. This simple and ubiquitous act has new relevance as humans venture into space, especially as it relates to the risk of DCS.

Astronauts performing EVAs, also called "space walks," from the U.S. Shuttle and International Space Station are at risk of getting DCS because of the decrease in ambient pressure from the spacecraft cabin to the space suit. In the shuttle, this is a change from 14.7 pounds per square inch absolute (psia) to 4.3 psia in the space suit. This depressurization can cause signs and symptoms of DCS if tissue nitrogen (N_2) partial pressure is not reduced through adequate denitrogenation before the depressurization, the EVA is several hours long, and the astronaut vigorously works during the EVA. Space walk during an EVA is a misnomer. Astronauts do not walk in the conventional sense but only anchor their legs to a stable structure so that the upper body can affect some task. We characterize the lack of movement and therefore the lack of dynamic forces in the lower body over several days of adaptation to microgravity and during EVAs as lower body adymania (LBA).

A series of experiments at the Johnson Space Center (JSC) designated ARGO I, II, and III (22,23) and one test at Duke University (27) were conducted to evaluate the role LBA as a factor to reduce the risk of DCS. We use statistical methods to test the hypothesis that LBA can reduce the risk of DCS and venous gas emboli (VGE). In other words, our null hypothesis is that these DCS and VGE data are no different compared with similar data collected under conditions where LBA was not a factor. We define LBA as restricted lower body movement, particularly walking or even a standing posture, during both the denitrogenation phase (prebreathing) at site

From the Life Sciences Research Laboratories, NASA-Johnson Space Center, Houston, TX.

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Address reprint requests to: Dr. Johnny Conkin, who is an Assistant Professor of Physiology affiliated with the National Space Biomedical Research Institute through Baylor College of Medicine, c/o Life Sciences Research Laboratories, NASA/Johnson Space Center/SD3, 2101 NASA Road 1, Houston, Texas 77058-3696; jconkin@ems.jsc.nasa.gov

pressure and during the exercise phase while at altitude.

METHODS

Our data come from the Hypobaric Decompression Sickness Databank (HDSD), a repository of data obtained from published reports concerning thousands of human exposures in altitude chambers that were performed from 1942 to the present (3). These data are coded and archived for easy retrieval by computer. The HDSD currently contains 456 records, each being the particulars of a unique test series that could have included as few as 1 exposure or as many as 47,000 exposures. Several identical exposures, usually with different people, form a test, and several identical tests form a record. Only 236 of the records, containing 4118 exposures, have data about the individuals. Within these 4118 exposures are 549 from the unpublished NASA HDSD maintained at JSC.

The type of information reported, both explanatory and response variables, about these tests dictates the analysis that is possible. For example, a survival analysis (SA) is appropriate if the time of a symptom or the time of first detection of VGE is included in a published report. A logistic regression (LR) would be appropriate if only the dichotomous DCS or VGE outcomes of different tests are reported. Three analyses are done to evaluate the effect of adynamia because no single approach utilizes all of the available information. Analysis I is an LR of DCS and VGE outcomes from group-data. Analysis II is a log logistic SA of DCS and VGE failure times from individual-data. Finally, Analysis III is an evaluation of a VGE response and recovery model using the same data as used in the SA. We used the SYSTAT Logit module [version 2.0, (25)] to fit parameters in the LR model, and the Nonlin module [version 5.03, (30)] to fit parameters in the log logistic survival model and the VGE response and recovery model.

Fundamental to understanding our methods and conclusions is to first understand how we calculate a simple decompression "dose" called the Tissue Ratio (TR), which is our continuous predictor variable in Analysis I. Tissue Ratio combines two important explanatory variables and is defined as the ratio of $P1N_2$ to P2, where $P1N_2$ is defined in Eq. 1 and P2 is the ambient pressure after ascent. Prebreathing 100% oxygen (O_2) or O_2-enriched mixtures prior to a hypobaric decompression is often used to prevent DCS, so it is necessary to account for the use of O_2-enriched mixtures prior to decompression. 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 theoretical tissue compartment after a specific time is:

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

where $P1N_2$ is the calculated N_2 partial pressure in the tissue after "t" minutes, P_0 is the initial N_2 partial pressure in the compartment, P_a is the ambient N_2 partial pressure in breathing mixture, and "t" is the time at the new P_a in minutes. The tissue rate constant "k" is equal to $\ln(2)/t_{1/2}$, where $t_{1/2}$ is the half-time for N_2 partial pressure in the 360 min compartment. 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. 1 simple. It is not our intent to develop a rigorous deterministic model for DCS or VGE, so all considerations of metabolic gases as they relate to DCS and VGE outcomes are ignored.

DCS and VGE Data for the Logistic Regression

Our challenge was to devise an analysis whereby the purported benefit of LBA to reduce the risk of DCS and VGE could be separated from the known benefit of being sedentary while at altitude. Typically, a person walks before and during an altitude exposure but is still classified as "inactive" or "sedentary" if no prescribed exercise was done. In other words, the premise is that LBA before and during the altitude exposure provides protection in excess of the protection already afforded due to inactivity while at altitude.

Three subsets of data were selected from the HDSD: Group "a" are those generally adynamic during the prebreathe but who walked in the chamber in a prescribed fashion from one exercise station to the next while at altitude (n = 876), Group "b" are also generally adynamic during the prebreathe but no exercise besides uncontrolled walking was performed at altitude (n = 449), and Group "c" are those with strict LBA during the prebreathe and while at altitude, but upper body exercise was performed (n = 76). The response (dependent) variables were the presence or absence of any sign or symptom of DCS and VGE. We excluded from consideration those cases where paresthesia was the only symptom during the test since not all investigators documented paresthesia in their reports. The Appendix contains a summary of the tests used in this analysis, and a list of references where other details about each test can be obtained.

Table I summarizes important variables in the three groups. Group "a" contains contemporary data collected from tests conducted at JSC (479 exposures) and Brooks Air Force Base (397 exposures from 7 published reports) from 1980 to 1990. On reaching the final test altitude, the subjects in Group "a" performed a variety of repetitive 4-min exercises, mostly while standing. They walked to as many as three exercise stations plus a VGE monitoring station over a repetitive 16-min cycle. The assigned exercises included a circuit of various combinations of stepping on a platform, rowing on a row machine, curling weights with the arms, standing at a torque station while using a torque-wrench on a series of fixed bolts, standing at a bicycle ergometer modified as a crank device for the upper body, and sitting at a rope pull device and pulling against a constant resistance. The exercises done by Group "c" were also a circuit of torquing a series of fixed bolts, cranking a bicycle ergometer, and pulling a rope against a constant resistance, but the circuit was performed from a

TABLE I. STATISTICAL SUMMARY OF DECOMPRESSION RECORDS.

Group	P2	±SD	Time	±SD	TR	±SD		# Tests	Exposures	DCS Cases
					DSC data (n = 1401)					
a (0, 1)*	6.61	2.01	5.25	1.67	1.44	0.25		36	876	96
b (0, 0)	5.90	1.57	4.37	2.46	1.46	0.28		29	449	34
c (1, 1)	4.97	1.02	3.50	0.64	1.80	0.07		4	76	8
means	6.29	1.89	4.88	1.98	1.46	0.27	totals	69	1401	138
					VGE data (n = 1166)					
a (0, 1)	6.61	2.01	5.25	1.67	1.44	0.25		36	875	304
b (0, 0)	5.49	1.50	5.06	2.82	1.46	0.27		20	215	51
c (1, 1)	4.97	1.02	3.49	0.64	1.80	0.07		4	76	19
means	6.30	1.95	5.10	1.94	1.46	0.26	totals	60	1166	374

SD is standard deviation; P2 is ambient pressure at altitude with psia units; time is elapsed time at P2 with h units; * (0 or 1 for adynamic condition before and during exposure, 0 or 1 for exercise condition during exposure).

seated or recumbent position, no walking was allowed. Additional details about the types of exercise and the metabolic cost of these activities are found elsewhere (4,7,17,22). The LBA data from Group "c" only contribute 6% of the total exposures in the LR analysis. All but ARGO III had repeat exposures where the subjects were ambulatory. The ambulatory results are included in the Group "a" data. Data from Group "b" are primarily historical since no laboratory at present is conducting experiments where subjects are inactive while at altitude. Of the 449 exposures from Group "b," 266 come from 6 published reports from 1944 to 1987, with the balance from the NASA HDSD. The three groups are shown separately in Table I, but the LR used all 1401 exposures from 69 tests in the DCS analysis and 1166 exposures from 60 tests in the VGE analysis. Nine tests in Group "b" did not have information about VGE since the ultrasound device to detect bubbles in the pulmonary artery was not always available. A salient point is that wide ranges of prebreathe times and final altitudes are included in the LR. For example, P2 ranges from 4.3 to 10.0 psia, and TR ranges from 0.94 to 2.28. Finally, both ambulatory and LBA data are shown in greater detail in **Table II**.

Analysis I: Logistic Regression

Equation 2 is the LR model expanded to include four explanatory variables.

$$P(\text{event}) = e(\beta_0 + \beta_1 x_1 + \cdots + \beta_4 x_4) \div [1 + e(\beta_0 + \beta_1 x_1 + \cdots + \beta_4 x_4)], \quad \text{Eq. 2}$$

where "event" is occurrence of DCS or VGE any time during the exposure, x_1 is [ln (TR–0.78)], x_2 is 0 for no LBA and 1 for LBA, x_3 is 0 for no exercise and 1 for exercise, x_4 is 0 for female and 1 for male, and the β_i are regression coefficients to be estimated from the data. The TR for each exposure depends on the prebreathe procedure through Eq. 1. Random walking by subjects in Group "b" was not considered "exercise," so they were coded LBA = 0 and exercise = 0. Notice that exposure time does not appear as a variable in Eq. 2. Table I shows that the mean exposure time for the groups is greater than 3 h. Decompression sickness and gas evolution are often seen before 3 h of exposure in these tests (4,6,17), therefore, we did not bias the results because of very short durations in any group, and did not use exposure time as a predictor variable in the logistic model. The assumption is that if DCS or VGE did not occur by the end of an exposure, then it would never have occurred had the exposure been extended.

DCS and VGE Data for the Survival Analysis

The elapsed time when DCS or VGE occurred is not part of the LR, only the number of DCS or VGE events that occurred during the test. An SA is possible if you

TABLE II. ADYNAMIA AND AMBULATORY DCS AND VGE DATA.

Test (reference)	n	Adynamia Duration (h)				TR	DCS Cases	VGE Cases	Adynamic Condition
		Before PB	During PB	At P2	P2				
ARGO I (3)	23	72	0	3	6.5	1.78	2	6	1
	24	0	0	0	6.5	1.78	1	12	0
ARGO II (3)	7	6	4.0	3	4.3	1.68	0	2	2
	11	0	4.0	0	4.3	1.68	3	5	0
ARGO III (3)	28	6	3.0	4	4.3	1.88	3	7	2
Duke (27)	18	0	3.5	4	4.3	1.77	3	4*	3
	19	0	3.5	0	4.3	1.77	12	9*	0

PB is prebreathe, * only VGE Grade ≥ II were reported in 18 subjects.
Adynamic condition "0" is included in Group "a" data and conditions 1, 2, and 3 are the Group "c" data.
0 = subjects were ambulatory before the PB and during the altitude exposure.
1 = subjects were recumbent before and during the altitude exposure.
2 = subjects sat before and during the altitude exposure.
3 = subjects sat during the prebreathe and then recumbent during the altitude exposure.

know when DCS or VGE occurs during an exposure. This is a powerful approach to evaluate the importance of LBA, and exposure time is now a variable. The SA models the P(failure time T ≤ t) as a function of exposure time "t" where failure time "T" is defined as the elapsed time from the beginning of a test after the ascent is complete to the first report of a DCS symptom, or the first detection of VGE. Failure times for DCS are considered exact since it is known exactly when a subject reports a symptom. On the other hand, the exact failure time for VGE is uncertain since there was a 12-min period of uncertainty when the data were not collected followed by a 4-min interval when these data were collected. However, we will consider the VGE data as exact failure time since the interval period is short and identical for all subjects. For exposures in which DCS or VGE did not occur, the censored time was recorded and used in the SA (9,18). Censored time is the elapsed time from the beginning of an exposure, after the ascent is complete, to the end of the exposure.

For Analysis II, we selected a subset of exposures from Group "a" and "c" that had failure times for DCS and VGE. We first selected records from tests done at JSC where LBA was the experimental variable. The mean TR for the 58 exposures was 1.82, with a narrow range from 1.68 to 1.88. To make a valid comparison to the ambulatory data, we then selected all records from tests done at JSC where LBA was not present and TR was greater than 1.70. There were 176 exposures available with a mean TR of 1.77 and a narrow range from 1.70 to 1.81. A total of 234 exposures from 16 tests is a reasonable sample size to evaluate. Any benefit ascribed to LBA in a comparison to ambulatory data is not confounded by TR since TR is not a variable. An ideal situation for the SA is that many tests covering a wide range of TRs with and without LBA would be available, but these data are not yet available.

Analysis II: Survival Analysis

Equation 3 is the cumulative distribution function of the log logistic survival model expanded to include LBA and gender effects.

$$P(T \le t) = 1 - 1/[1 + (1 + (\beta_1 x_1))(1 + (\beta_2 x_2))(t\rho)^{\lambda}], \quad \text{Eq. 3}$$

where "T" denotes the failure time to DCS or VGE during the altitude exposure, "t" is time at altitude ranging to 4 h, x_1 is 0 for no LBA and 1 for LBA, and x_2 is 0 for female and 1 for male. The parameters β_n, ρ, and λ are optimized to maximize the likelihood associated with the modeled probability distribution. Additional details to fully describe the log logistic survival model and maximum likelihood estimation are available elsewhere (4,9,18).

Data for the VGE Response and Recovery Model

Analyses I and II model the probability of occurrence or the distribution of the time of occurrence of VGE. However, there is additional information about how the incidence of VGE changes through time that can be used to evaluate adynamia. Ultrasonic bubble monitoring over the pulmonary artery was performed about every 12 min over a 4-min period in tests whose duration was 3–4 h. While in a supine or seated position, the subject was instructed to flex each limb in turn three times to dislodge VGE from the tissue capillaries and facilitate VGE detection and grading. The audio, and sometimes video, signals from a bubble detector were used by trained observers to assign a grade for VGE from each limb on the 0–4 Spencer scale (24). There were from 12 to 15 VGE measurement periods in an exposure, depending on the length of an exposure, and a VGE grade was assigned to each of the four limbs during each measurement period. The Grade of VGE was later converted to a binary code, "0" for Grade zero and "1" for Grades I through IV. This is also how the VGE data were transformed for Analyses I and II. To make the statistical regressions manageable, the mean time for each VGE measurement period, not the actual time for each subject, is associated with the number of "1" and "0" responses during the measurement period. The number of subjects with VGE is divided by the total number of subjects at a particular VGE measurement period to calculate the fraction of the sample with VGE associated with each limb. Since all tests were at least 3 h in duration, the curves on the figures to follow are well defined for the first 3 h.

Analysis III: VGE Response and Recovery Model

We previously developed a function (6) that combined a response process and a recovery process to characterize the time course in the occurrence of VGE. Eq. 4 characterizes the incidence of VGE as a function of time.

$$\text{VGE incidence} = [t^{\alpha}/(t^{\alpha} + p_{50}^{\alpha})](e^{(-\gamma t)}). \quad \text{Eq. 4}$$

The three parameters (α, p_{50}, and γ) are adjusted during the computerized fitting process until they maximize the agreement between the predicted VGE incidence from Eq. 4 and the observed incidence from the data.

RESULTS

Analysis I: Logistic Regression

Table III shows the parameter estimates, standard errors, p values, and odds ratios for the DCS and VGE LR models.

The negative sign on the LBA estimate in both models means that the P(DCS) and P(VGE) are reduced when LBA is present. The odds ratio is the ratio of odds of DCS and VGE for LBA = 1 to the odds for LBA = 0, estimated to be 0.31 and 0.21 for the respective models. Because of our LBA coding convention, the smaller the odds ratio, the stronger the effect. A person decreases the odds by a factor of about three (1/0.31) for DCS and about five (1/0.21) for VGE when LBA is present. P values < 0.01 for each parameter estimate indicates LBA significantly reduces the odds of DCS and VGE. For example, in a simulation of a 3-h O_2 prebreathe prior to ascent to 4.3 psia for a 4-h exposure the calculated TR is 1.907 (application of Eq. 1 and definition of TR). The P(DCS) that follows from Eq. 2 decreases from 0.33 in subjects who are ambulatory and exercise the

TABLE III. PARAMETER ESTIMATES FOR DCS AND VGE LOGISTIC REGRESSION MODELS.

Parameter	Estimate	SE	Estimate/SE	p Value	Odds Ratio (95% range)
			DCS model (n = 1401)		
β_0 (constant)	−1.662	0.193	−8.60	<0.01	n/a
β_1 [ln(TR − 0.78)]	3.149	0.349	9.01	<0.01	23.3 (46.2 to 11.7)
β_2 (LBA)	−1.156	0.400	−2.89	<0.01	0.31 (0.69 to 0.14)
β_3 (exercise)	0.586	0.222	2.64	<0.01	1.80 (2.7 to 1.16)
			VGE model (n = 1166)		
β_0 (constant)	−0.658	0.242	−2.72	<0.01	n/a
β_1 [ln(TR − 0.78)]	2.397	0.214	11.21	<0.01	11.0 (16.7 to 7.2)
β_2 (LBA)	−1.512	0.290	−5.32	<0.01	0.21 (0.38 to 0.12)
β_3 (exercise)	0.706	0.189	3.73	<0.01	2.02 (2.93 to 1.40)
β_4 (gender)	0.457	0.172	2.66	<0.01	1.58 (2.21 to 1.13)

SE is the asymptotic standard error. If the p value is ≤ 0.05, then we reject the null hypothesis that the estimate equals zero.

upper body to 0.13 in those who are adynamic but also exercise the upper body. The P(VGE) in males decreases from 0.69 to 0.32. This simulation is a typical profile tested at JSC. Our simulated results are similar to observed results from the ARGO III test (see Test 68 in Appendix) for the adynamic condition.

The addition of gender improved the VGE model, but not the DCS model. Females contributed 299 of the 1401 exposures used in the DCS analysis and 282 of the 1166 exposures used in the VGE analysis. Females are 1.6 times less likely to have VGE compared with males under otherwise comparable conditions. The log likelihood (LL) number improved from 451 for a constant-only DCS model (the null model) to 389 with the addition of the three explanatory variables, and the LBA variable improved the model by 5 LL units. The LL number improved from 732 for a constant-only VGE model to 630 with the addition of the four explanatory variables, the LBA variable improved the model by 16 LL units. We report the absolute value of the LL number, and a smaller number indicates better agreement between predicted and observed. Finally, the addition of the planned altitude exposure time did not improve either the DCS or VGE models ($p > 0.05$ for the parameter and LL did not significantly improve). This was expected since the average exposure time in the data set was greater than 3 h (see Table I).

Fig. 1 shows the P(DCS) in simulations using Eq. 2 together with the parameter estimates in Table III under three conditions: subjects who both exercised the upper body and were ambulatory at altitude (Group "a"), subjects who did no exercise but were ambulatory at altitude (Group "b"), and subjects who both exercised the upper body and were adynamic before and during the altitude exposure (Group "c").

The middle solid curve shows the P(DCS) for a given TR for subjects who did not exercise but were ambulatory is greater than for subjects who did exercise the upper body but were adynamic before and during the altitude exposure (lower solid curve). Therefore, the best estimate of DCS risk is reduced to below the risk afforded through inactivity by including LBA. The 95% confidence interval (CI) for the lower curve is included. The upper CI does overlap the curve for Group "b". Therefore, a conservative conclusion is that LBA, over a narrow range of TR, that included upper body exercise is as protective against DCS as random walking by subjects who did no prescribed exercise while at altitude.

One way to assess the goodness-of-fit of the DCS model is to compare the observed DCS cases with the predicted cases using the explanatory data in the three subsets of data used to parameterize the model. The observation of DCS is always yes (1) or no (0), and the predicted is always between these extremes. The goodness of fit from any single observation is meaningless since no one expresses a symptom between zero and one. However, the sum of probabilities over all exposures gives an indication of how well the model accounts for the observations. Group "a" had 96 cases of DCS in 876 exposures (see Table

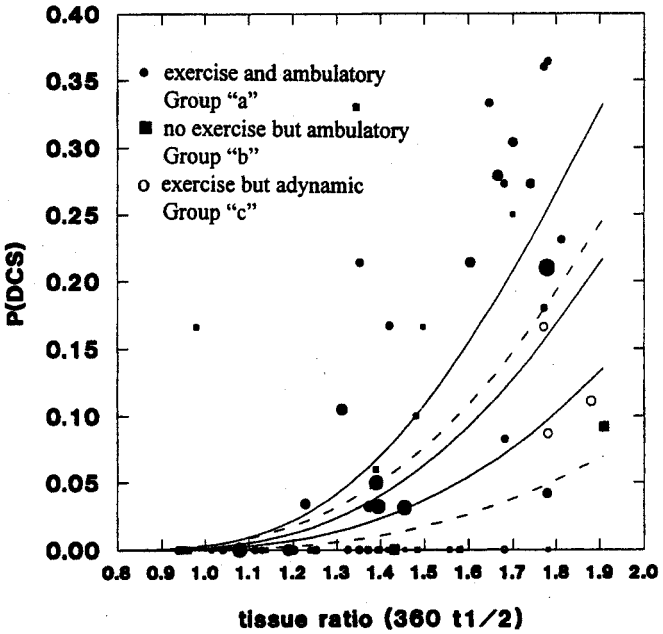

Fig. 1. P(DCS) as a function of TR in the logistic model. The upper curve is for the conditions Exercise = 1 and LBA = 0, the middle curve is Exercise = 0 and LBA = 0, and the lower curve is Exercise = 1 and LBA = 1. These are the three conditions represented in the data. The size of the symbols is proportional to the number of people in a test. The solid curves come from simulations after the model was optimized to all 1401 exposures. The dashed curves are the upper and lower 95% CI for the LBA curve. Two squares (Tests 44 and 46 in the Appendix) and one filled circle (Test 36 in the Appendix) are not on the graph due to the y-scale, but were not excluded from the regression.

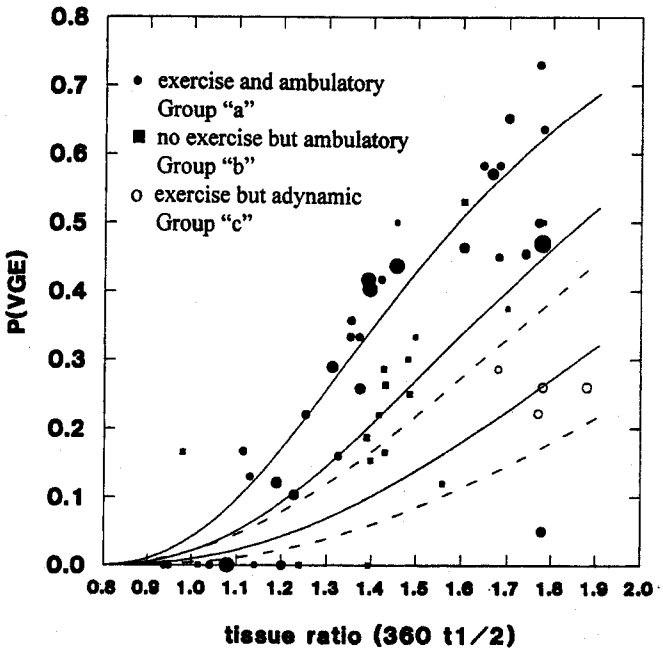

Fig. 2. P(VGE) as a function of TR in the logistic model under the same conditions as in Fig. 1, plus male gender is specified. The dashed curves are the upper and lower 95% CI for the LBA curve. The overlap of the CI (not shown) is not as evident as in Fig. 1. The contribution of LBA to reduce the incidence of VGE is more pronounced than for the DCS data. Two filled circles (Tests 2 and 3 in the Appendix) are not on the graph due to the y-scale, but were not excluded from the regression.

I). The summation of the probabilities from the model was 96.0. Group "b" had 34 cases in 449 exposures with 34.0 cases predicted, and Group "c" had 8 cases with 8.0 cases predicted. The logistic model for DCS with only four variables (exercise, adynamia, P2 and $P1N_2$) did not over or under predict the observed cases of DCS.

Fig. 2 shows the P(VGE) in simulations using Eq. 2 together with the parameter estimates in Table III under the same three conditions as above, plus male gender is specified since gender is an explanatory variable in the VGE model.

Again, to reduce the risk of VGE below the risk for ambulatory subjects who do no prescribed exercise requires that adynamia be included. Here is a strong case to conclude that LBA, over a narrow range of TR, that included upper body exercise is more protective against VGE than random walking by the subject that did no prescribed exercise while at altitude. When female gender is specified as part of the adynamia simulation the best estimate of P(VGE) runs parallel to the lower CI on Fig. 2. The number of observed VGE cases compared with the predicted cases were as follows: Group "a" had 304 cases of VGE in 875 exposures (see Table I). The summation of the probabilities from the model was 303.9. Group "b" had 51 cases in 215 exposures with 51.0 cases predicted, and Group "c" had 19 cases with 18.3 cases predicted. The logistic model for VGE with five variables (exercise, gender, adynamia, P2 and $P1N_2$) did not over or under predict the observed cases of VGE.

Analysis II: Survival Analysis

Table IV shows the parameter estimates, standard errors, and p values for the DCS and VGE survival models. We added weight, gender, and TR to the models to test if these variables contributed to the models. They did not contribute to the DCS model, and neither weight nor TR improved the VGE model. However, the LL number for the VGE model (260.4) that included gender and adynamia did improve significantly over the model (264.8) with just adynamia, a $p < 0.01$ for a χ^2 value of 8.84 and one degree of freedom. We use the Likelihood Ratio Test (4,18) as the basis for our conclusions. The 3° of freedom for DCS and 4° of freedom for VGE were adequate to describe most of the available data. Recall that all subjects in the subset of data from Groups "a" and "c" exercised while at altitude and that TR had a narrow range from 1.68 to 1.88.

The mean DCS failure time and standard deviation (SD) in hours is slightly greater in the adynamic subjects (2.13 ± 0.84 SD, $n = 5$) compared with ambulatory subjects (1.63 ± 0.79, $n = 39$), but not statistically different at $p = 0.20$ from an unpaired *t*-test. The mean VGE failure time is greater in the adynamic subjects (1.46 ± 0.85, $n = 15$ vs. 0.97 ± 0.60, $n = 97$) with $p < 0.05$. However, the strict requirement for independence between the adynamic and ambulatory groups to use the *t*-test is not met. So we removed those VGE failure times from the data set of ambulatory subjects if the same subject appeared in the adynamic group or if an ambulatory subject participated in more than one ambulatory test. There were 35 records excluded, and the mean VGE failure time was still greater in the adynamic subjects (1.46 ± 0.85, $n = 15$ vs. 0.98 ± 0.62, $n = 62$) with $p = 0.07$.

Table IV shows that the LBA parameter for both the DCS and VGE models was important enough to include. However, the mean failure time for DCS was not statistically greater for the adynamic subjects. The Mantel-Haenszel Test evaluates a possible difference between two survival curves, curves from the non-parametric Kaplan-Meier after stratifying the failure times into those that ambulated and those that were adynamic. The Mantel-Haenszel Test provides a model-independent assessment for the significance of LBA. There were 39 DCS failure times in 176 subjects who ambulated while in the chamber, and 5 DCS failure

TABLE IV. PARAMETER ESTIMATES FOR LOG LOGISTIC SURVIVAL MODELS.

Parameter	Estimate	SE	Estimate/SE	p Value
DCS model (n = 234)*				
λ (index)	1.524	0.2105	7.24	<0.01
ρ (scale)	0.144	0.0247	5.72	<0.01
β_1 (LBA)	−0.717	0.1421	−5.04	<0.01
VGE model (n = 234)				
λ (index)	1.176	0.0962	12.22	<0.01
ρ (scale)	0.222	0.0621	3.57	<0.01
β_1 (LBA)	−0.734	0.0897	−8.18	<0.01
β_2 (gender)	1.639	0.9010	1.82	0.07

* Only 44 of the 45 cases of DCS were used in the DCS model since the failure time was not available for one case.

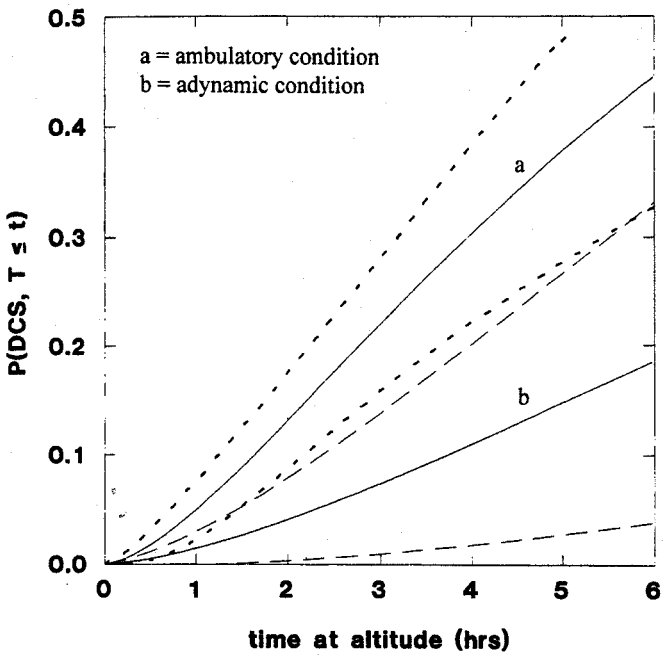

Fig. 3. P(DCS, T ≤ t) as a function of time at altitude for two simulations with the log logistic survival model. The lower curve is with LBA = 1 and the upper curve is with LBA = 0. The dashed curves are 95% CI for each curve. Notice the intervals are wide but do not overlap over most of the simulation. Recall that all the subjects exercised while at altitude. The adynamic subjects also exercised the upper body while the ambulatory subjects exercised the upper body and walked from place to place in the altitude chamber.

times in the 58 subjects who were adynamic. The test gave a χ^2 of 0.61 with 1° of freedom, and p = 0.43. Even though the parameter for LBA was a significant contribution to the DCS survival model, the comparison of two non-parametric survival curves shows that the failure times with and without LBA are statistically indistinguishable. A trend is evident, but there are too few failure times in adynamic subjects to properly evaluate. The VGE analysis may support this conclusion. Here only VGE failure times for males were used because a simulation to follow is specific for males. There were 86 VGE failure times in 145 males that ambulated while in the chamber, and 11 failure times in 36 males that were adynamic. The test gave a χ^2 of 7.77 with 1° of freedom, and p = 0.005. Again, the parameter for LBA was a significant contribution to the VGE survival model, but in this comparison of two non-parametric survival curves, the failure times with and without LBA are statistically distinguishable. The trend is for VGE and DCS symptoms to come later in the adynamic subjects. The proportion of DCS (8.6%, 5/58) is lower in the adynamic subjects compared with the ambulatory subjects (22%, 39/176) as well as the proportion of VGE (26%, 15/58 vs. 55%, 97/176). Finally, adynamic females were well represented, being a greater proportion of the sample compared with the ambulatory females (38%, 22/58 vs. 17.5%, 31/176).

Fig. 3 shows the P(DCS, T ≤ t) as a function of time at altitude using Eq. 3 together with the DCS parameter estimates in Table IV in simulations under two conditions: subjects were ambulatory at altitude or subjects were adynamic before and during the altitude exposure. **Fig. 4** shows the P(VGE, T ≤ t) using Eq. 3 with the VGE parameter estimates in **Table V** under the same conditions used in Fig. 3, plus male gender was specified in the simulation.

The 95% CI for the DCS and VGE adynamia curves do not overlap the intervals for the ambulatory curves. Given a TR between 1.68 and 1.88, a subject is less likely to have DCS or VGE if he is adynamic while still doing exercise with the upper body compared with subjects walking from place to place while also doing exercise with the upper body. There were 45 cases of DCS observed in 234 exposures, and the DCS model predicted 27.7 cases. There were 112 cases of VGE observed in the same set of data, and the VGE model predicted 84.3 cases. Compared with the earlier logistic regressions, the survival models for DCS and VGE with fewer explanatory variables under predicted the observations. A greater proportion of under estimation was from the 176 exposures where ambulation was a variable. Here 40 cases of DCS were observed, with 23.6 predicted. There were 97 cases of VGE with 71.4 predicted. The 58 exposures with adynamia were reasonably described: 5 cases of DCS observed with 4.1 predicted, and 15 cases of VGE observed with 12.9 predicted.

Table V shows the number and location of the first symptom(s) (or sign) of DCS reported by adynamic and ambulatory subjects. In those cases where multiple symptoms were first reported, all were included in Table V. We also show, for completeness, the number and location of subsequent symptoms. However, most tests that included ambulation were not terminated once DCS was diagnosed. They were allowed to continue until reaching a well-defined termination point. The tests that included adynamia were terminated at the time DCS was first diagnosed. So it is not possible to use the additional information in the parentheses in a

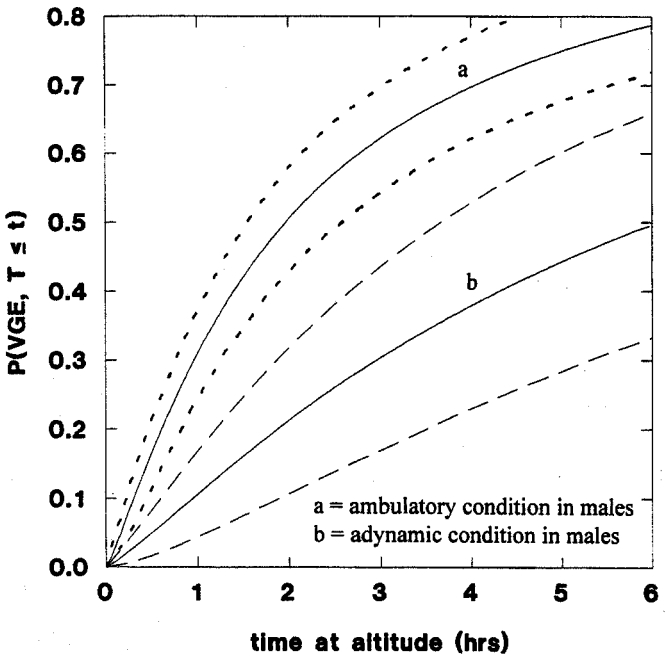

Fig. 4. P(VGE, T ≤ t) as a function of time at altitude for two simulations with the log logistic survival model. The lower curve is with LBA = 1 and gender = 1. The upper curve is with LBA = 0 and gender = 1. The 95% CI for each curve do not overlap.

TABLE V. LOCATION OF FIRST DCS SIGN OR SYMPTOM.

Location of Symptom	Adynamia Cases (n = 58 Exposures)	Ambulatory Cases (n = 176 Exposures)
	Lower Body Locations	
1. right knee	2	8 (5)
2. left knee	1	7 (2)
3. right and left knee		4
4. right foot		1 (2)
5. left foot		1
6. right calf		1
7. left calf		1
8. right ankle		2 (2)
9. left ankle		1 (1)
10. right leg		1
11. right ankle and knee		1
12. left ankle and knee		1
	Upper Body Locations	
13. right wrist	1	1
14. left wrist	(1)	
15. pain behind right eye		(1)
16. headache		(2)
17. dizziness		(1)
18. skin mottling on chest	1	1
19. left shoulder		1
20. right shoulder		(1)
21. right arm		1
22. left ring finger		1
23. left hand		1
24. right hand		1
25. left elbow		1
26. right elbow		1
27. right thumb		1

( ) is the number of DCS symptoms after the first symptom.

comparison of results between tests with adynamia and those that permitted ambulation. The best opportunity to evaluate the influence of adynamia is to compare the numbers and locations of the first symptom(s). It is clear that even adynamic subjects can have "pain-only" DCS symptoms in the lower body. A Fisher's Exact χ^2 test shows there is no difference between the 60% symptoms (3/5) observed in the lower body of the adynamic subjects and the 74% symptoms (29/39) observed in the ambulatory subjects ($p = 0.42$). The lower body is the dominant location of pain-only symptoms. Lower Body Adynamia appears to reduce the total incidence but does not change the distribution of symptoms, at least in this small sample of data.

Analysis III: VGE Response and Recovery Model

Table VI shows the parameter estimates and standard errors for the VGE response and recovery model (Eq. 4) for each of the body limbs for the adynamic and ambulatory subjects. The mean TR for the adynamic subjects was 1.82 ± 0.07 SD and 1.77 ± 0.02 SD for the ambulatory subjects. The information in Table VI is best summarized in figures.

Fig. 5 shows the fraction of VGE from the right leg between ambulatory and adynamic subjects during the altitude exposure. The two solid curves come from evaluating Eq. 4 given the estimates for the parameters in Table VI for the right leg. The change in slope during the response phase of the ambulatory subjects is greater than that of the adynamic subjects. For most of the time at altitude, the fraction of VGE from the right leg is higher in ambulatory subjects. Our regression approach does not account for the fact that the observations are dependent. By dependent we mean one person is monitored 12 to 15 times during the course of the exposure. The standard errors for the parameters and resulting CIs are small because we assume 2004 independent measurements and do not consider the 176 persons these measurements came from, in the case of the upper curve in Fig. 5. For this reason, we do not show CIs for the best-fit curves.

Fig. 6 includes the curves from Fig. 5 and also the curves for the other three limbs. Notice the similarity of all the solid curves from the adynamic subjects compared with the divergence in two of the dashed curves for the ambulatory subjects. The upper dashed curves are from the left and right legs while the lower dashed curves are from the left and right arms. In addition to the magnitude of the difference there is also a greater separation between the arms and legs in the ambulatory subjects compared with the adynamic subjects. Clearly, walking in an altitude chamber increases the likelihood of forming VGE, which are eventually transported from the tissues into the lungs.

Finally, the p_{50} numbers in Table VI are used to characterize the differences in the two samples. The p_{50}

TABLE VI. PARAMETER ESTIMATES FOR VGE RESPONSE AND RECOVERY MODEL.

Parameter	Adynamia			Ambulatory		
	γ (Rate)	α (Shape)	P_{50}	γ (Rate)	α (Shape)	P_{50}
Right leg						
Estimate	0.00629	1.4989	249.71	0.00446	1.7682	79.50
SE	0.00320	0.5565	168.81	0.00054	0.1987	7.365
Left leg						
Estimate	0.00596	1.5819	284.37	0.00462	1.9791	80.12
SE	0.00386	0.6613	225.65	0.00055	0.2265	6.977
Right arm						
Estimate	0.01127	1.7641	147.55	0.00799	1.7810	103.86
SE	0.00267	0.5627	63.076	0.00103	0.2650	16.526
Left arm						
Estimate	0.00599	1.3859	443.60	0.00774	2.1297	136.74
SE	0.00541	0.7355	581.26	0.00141	0.3746	26.548

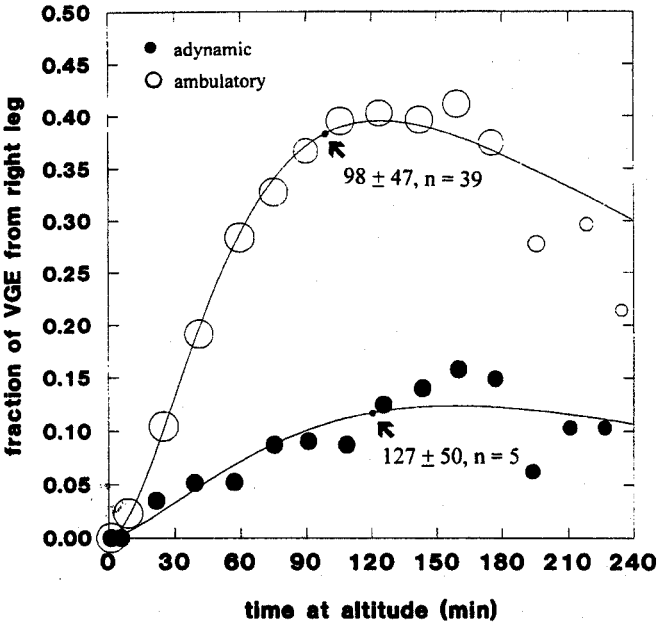

Fig. 5. Comparison of the time of occurrence of VGE from the right leg between ambulatory (open circles) and adynamic (filled circles) subjects. VGE were detected in the pulmonary artery after the right leg was flexed. The area of a circle is proportional to the number of exposures that contributed to the fraction of VGE at a particular time. Arrows on each curve locate the mean time to report any symptom of DCS, regardless of the anatomical location of the symptom (see Table V).

for each leg in the adynamic subjects is three times greater than for the ambulatory subjects (about 240 min vs. about 80 min). P_{50} defines where along the x-axis you will observe 50% of the response along the y-axis. In other words, to get 50% VGE in the response function of Eq. 4 $[t^a/(t^a + p_{50}{}^a)]$ would theoretically require triple the time in the adynamia model compared with the ambulatory model. The p_{50} for each arm in both groups is more variable. Often VGE assigned to the arms have their origins in the legs, plus the arms do not contribute as much VGE information as the legs. It is difficult to keep the legs inactive while the arms are being flexed during the VGE monitoring period, thus distorting the information from the arms.

DISCUSSION

The three analyses used on the limited LBA data suggest that LBA is a technique of sufficient magnitude to reduce the risk of DCS and VGE. A person who is inactive, more specifically neither standing erect nor walking, before and during a prebreathe and while at altitude is less likely to have DCS or VGE than the same person who is inactive at altitude but walks before and during the exposure. The mean latency times of the first symptom and VGE are extended in adynamic subjects compared with ambulatory subjects. We feel there is enough data to recommend LBA as a technique to use before and during an altitude exposure if the goal is to reduce the risk of DCS and VGE, or reduce the variability in the DCS and VGE outcome for some people. We cannot say that adynamia before or during the exposure is more important since these data are not yet available. We reiterate that adynamia was present before or during the prebreathe and during the exposure in the Group "c" data (see Table II). Our working hypothesis is that any benefit derived from adynamia before an exposure is lost if the adynamia is not maintained during the exposure. A 2-, 3-, or 4-h prebreathe may be an adequate adynamic period if subjects continue the adynamia into the altitude exposure. The benefits attributed to long prebreathes may, in part, be related to reducing the size or number of micronuclei during the adynamic period (26). If adynamia is important, then this is one inter- and intra-subject variable responsible for the random nature of DCS. When adynamia is controlled, other variables that influence susceptibility to DCS could be better studied.

The statistical approaches used here simply summarize and compare data. The fundamental question about mechanisms to account for the observations cannot be answered with these data. We observe macroscopic outcomes and then infer mechanisms on a microscopic scale. A comprehensive review and discussion of micronuclei is beyond the scope of this report, but information is available (13,14,23). The fundamental untested premise of adynamia concerns the control of nucleation processes within tissues and fluids. In the absence of supersaturation (the difference between dissolved gas partial pressure and the absolute pressure), 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 prebreathe reduces, not increases, the incidence of DCS

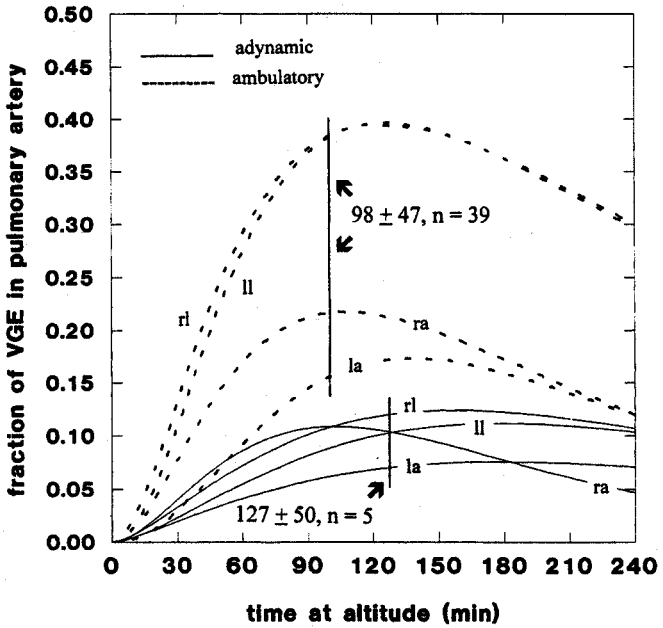

Fig. 6. Fraction of ambulatory (dashed curves) and adynamic (solid curves) subjects where VGE were detected in the pulmonary artery after limb flexion of different limbs. The mean time to report any symptom of DCS is identified with arrows, and it occurs just prior to the peak of maximum VGE incidence from the limbs. The values of the parameters in Eq. 4 to produce the curves are in Table VI.

and VGE (19,29). 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.

There are at least four areas that we contemplate when considering micronuclei: the rate of micronuclei formation, the number of micronuclei formed, the distribution of micronuclei size, and the rate of micronuclei dissolution, which includes mechanisms to stabilize micronuclei. Each of these processes is complex to characterize in a physical system and more so when energy is added to or subtracted from a biological system. For example, the mechanical energy transferred through tendons and ligaments from muscle contractions. Supersaturation could be tolerated indefinitely if the rate of nucleation or rate of bubble growth were very slow. Therefore, the full potential for evolved gas would not be realized if the supersaturation is reduced by the blood's removal of gas faster than either the rate of nucleation or the rate of bubble growth. The rate of nucleation for a given supersaturation may not be a rate-limiting step in bubble formation because there may be stabilized or easily formed micronuclei that exist in the body. Thus, the appearance of bubbles after decompression may depend simply on the growth of readily available micronuclei, and well-controlled experiments can help to resolve the mechanism(s) of adynamia. Viscous adhesion or tribonucleation (11,12,16,20), either before or after a decompression, is a process that could increase the rate of nucleation in living tissue and fluids, so experiments about micronuclei before a decompression should eliminate tribonucleation as a variable after the decompression. To complete the discussion, there is evidence that preformed and stabilized micronuclei do not exist before decompression, at least in a species of translucent crab (14,21).

We postulate that with an adynamic period of several hours, a new distribution of micronuclei are established such that fewer micronuclei transform into growing bubbles for a given supersaturation. The application of a high pressure spike, either hydraulic or pneumatic, filtration, or ultracentrifugation of a sample, are all accepted means to reduce the number and size of micronuclei (change the distribution) as evident by fewer bubbles or cases of DCS after a subsequent decompression (11,16,28). The idea of "using up" micronuclei faster than they are generated as a means to understand increased resistance to DCS on repeated exposures has also been discussed (13).

Our approach–to use LBA to reduce or otherwise control hypothetical micronuclei populations—appears to be the first use of this concept, especially as it applies to decompressions in microgravity. Violent muscular contractions in bullfrogs prior to hypobaric decompressions (31) were associated with bubble formation in the resting animals while at altitude, and has been known since 1945. The number of bubbles was reduced if the frogs were allowed to recover as long as 1 h after electrical stimulations. The authors offered two explanations: a short-lived local increase in carbon dioxide that facilitated bubble growth at altitude, or the inception of micronuclei or some other short-lived entity that would later facilitate the growth of bubbles at altitude. This same concept was recently tested in humans (10) where 20 subjects were exposed to 6.2 psia on 3 separate and random occasions without the confounding of prebreathe or any exercise at altitude during a 2-h exposure. Each subject did 150 deep knee bends in 10 mins either 2 h, 1 h, or just prior to ascent with the remaining time spent adynamic in a chair. As with the frogs, it was hypothesized that exercise before decompression would generate a population of some entity (micronuclei, macronuclei, vapor-filled cavities trapped on vascular endothelium, or increase the concentration of carbon dioxide) that would diminish in size or concentration given enough time prior to ascent. They used subsequent VGE information to indirectly test the hypothesis. They observed that intense lower body activity just prior to the altitude exposure did cause more VGE to appear, and to appear earlier compared with when exercise was done earlier. The critical observation was that the predisposing factor(s) diminished with time while sitting quietly in a chair prior to the ascent.

Lower body adynamia to reduce the risk of DCS, possibly by reducing the number and size of micronuclei, may have a limited utility in many situations but is important when relating DCS results obtained in altitude chambers to astronauts during EVA. Astronauts do not use the lower body the same in space as they do on Earth. They are generally adynamic for several days prior to and during an EVA. A more descriptive term is "abaroferric," used to describe both the lack of physical activity in the legs and the unloading of weight in the legs during the exposure to microgravity, which may be particularly important as a physical condition during EVAs. Indirect evidence suggests that astronauts and cosmonauts may have benefited from LBA since there has never been a report of DCS during an EVA. We acknowledge that underreporting can be attributed to additional factors that mask a minor pain-only symptom while in a space suit. Also, a bias not to report any problems in an operational setting should be acknowledged, and is a constant concern to Flight Surgeons (1). Finally, tissue denitrogenation might be enhanced in microgravity. If N_2 is not available to "grow" micronuclei, then factors that influence micronuclei become irrelevant. There are plans to use an automated Doppler bubble detector within a space suit to provide information about VGE during EVAs. These data will help to accurately define the risk of gas embolization and DCS, and to increase our understanding of the role of LBA to reduce the risk of DCS.

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APPENDIX: TABULATION OF SOME DATA USED IN ANALYSES.

Test #	Male (n)	Female (n)	Tissue Ratio	Exercise	Adynamia	Incidence of DCS	Incidence of VGE	Reference
				Group "a" Data				
1 +	11	0	1.780	1	0	0.364	0.636	A3*
2 +	13	0	1.812	1	0	0.231	0.846	A3*
3 +	3	0	1.701	1	0	0.667	1.000	A3*
4	12	0	1.646	1	0	0.333	0.583	A3*
5	23	0	1.700	1	0	0.304	0.652	A20*
6 +	22	0	1.740	1	0	0.273	0.455	A3*
7	28	0	1.604	1	0	0.214	0.464	A20*
8	14	0	1.353	1	0	0.214	0.357	A3*
9	35	0	1.665	1	0	0.279	0.571	A3*
10	12	0	1.420	1	0	0.167	0.417	A3*
11	12	0	1.681	1	0	0.083	0.583	A4*
12	12	0	1.113	1	0	0	0.167	A4*
13	12	0	1.371	1	0	0	0.333	A4*
14	12	0	0.948	1	0	0	0	A4*
15	12	0	1.351	1	0	0	0.333	A4*
16	12	0	0.938	1	0	0	0	A4*
17	19	19	1.311	1	0	0.105	0.289	A20*
18	11	0	1.040	1	0	0	0	A20*
19	15	14	1.227	1	0	0.034	0.103	A4*
20 +	59	22	1.778	1	0	0.210	0.470	A13*
21	32	32	1.454	1	0	0.031	0.437	A7

APPENDIX. CONTINUED.

Test #	Male (n)	Female (n)	Tissue Ratio	Exercise	Adynamia	Incidence of DCS	Incidence of VGE	Reference
22	31	31	1.394	1	0	0.032	0.403	A9
23	31	29	1.390	1	0	0.050	0.417	A7,A9
24	16	0	1.252	1	0	0	0.220	A12
25	8	0	1.128	1	0	0	0.130	A12
26	9	0	1.325	1	0	0	0.160	A12
27	26	11	1.188	1	0	0	0.121	A21,A8
28	20	11	1.373	1	0	0.032	0.258	A18
29	12	11	1.200	1	0	0	0	A22
30	12	10	1.086	1	0	0	0	A22
31	35	30	1.078	1	0	0	0	A22
32 +	11	0	1.771	1	0	0.360	0.730	A5*
33 +	11	0	1.771	1	0	0.180	0.730	A5*
34 +	15	9	1.778	1	0	0.042	0.500	A17*
35	9	2	1.680	1	0	0.273	0.450	A15,A16*
36	19	0	1.770	1	0	0.631	0.500++	A19
				Group "b" Data				
37	54	0	1.91	0	0	0.092	no data	A4*
38	21	0	1.345	0	0	0.330	no data	A6
39	31	0	0.961	0	0	0	no data	A6
40	57	0	1.431	0	0	0	no data	A6
41	18	0	1.239	0	0	0	0	A6
42	15	0	1.242	0	0	0	no data	A1
43	15	0	1.58	0	0	0	no data	A14
44	14	0	2.282	0	0	0.570	0.500	A14
45	8	0	1.70	0	0	0.250	0.375	A11
46	17	0	1.604	0	0	0.410	0.530	A3*
47	10	0	1.481	0	0	0.100	0.300	A3*
48	8	0	1.558	0	0	0	0.120	A3*
49	16	0	1.389	0	0	0.060	0.187	A3*
50	12	0	1.429	0	0	0	0.166	A3*
51	12	0	0.979	0	0	0.166	0.166	A4*
52	12	0	1.485	0	0	0	0.250	A3*
53	0	6	1.497	0	0	0.166	0.333	A3*
54	0	5	1.014	0	0	0	0	A3*
55	5	0	1.139	0	0	0	0	A3*
56	9	0	1.416	0	0	0	0.220	A5*
57	0	2	1.455	0	0	0	0.500	A5*
58	19	0	1.43	0	0	0	0.263	A5*
59	0	14	1.427	0	0	0	0.286	A5*
60	4	0	1.78	0	0	0	0.500	A4*
61	23	0	1.396	0	0	0	no data	A10
62	12	0	1.396	0	0	0	no data	A10
63	0	6	1.393	0	0	0	no data	A2
64	11	0	1.392	0	0	0	0	A17*
65	0	13	1.397	0	0	0	0.154	A17*
				Group "c" Data				
66 +	14	9	1.780	1	1	0.087	0.260	A17*
67 +	6	1	1.680	1	1	0	0.286	A15,A16*
68 +	16	12	1.880	1	1	0.111	0.260	A15,A16*
69	18	0	1.770	1	1	0.166	0.222	A19

These data and additional data about the individuals in each test are in the Hypobaric Decompression Sickness Databank referenced in the main report (3). Refer to Table I for additional summary information. Other data for some tests are in the NASA Hypobaric Decompression Sickness Databank, identified here with a * symbol. The NASA databank is an unpublished compilation of 549 human exposures collected from hypobaric DCS research done at the Johnson Space Center from 1983 to 1998. The symbol + identifies the tests that provided 234 exposures for analyses II and III. The ++ symbol indicates that only VGE Grade > II was reported, and only in 18 of the subjects.

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