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RESEARCH AND DEVELOPMENT OF ANTI-G LIFE SUPPORT SYSTEMS:

Part 2. Decompression Sickness Research

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NOTICES

This final report was submitted by the Life Sciences Division, Technology Incorporated, 300 Breesport, San Antonio, Texas 78216, under contract F33615-81-C-0600, job order 7930-14-42, with the USAF School of Aerospace Medicine, Human Systems Division, AFSC, Brooks Air Force Base, Texas. Larry J. Meeker (USAFSAM/VNS) was the Laboratory Project Scientist-in-Charge.

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The voluntary informed consent of the subjects used in this research was obtained in accordance with AFR 169-3.

The Office of Public Affairs has reviewed this report, and it is releasable to the National Technical Information Service, where it will be available to the general public, including foreign nationals.

This report has been reviewed and is approved for publication.

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Instrumentation and techniques for differentiating bends-prone and bends-resistant individuals were developed. Studies were conducted to determine bends- and bubble-formation altitudes using a variety of simulated pressure-suit pressures and breathing gas mixtures. A pressure of 9.5 psia eliminated the occurrence of bends under the conditions of these studies. In vitro studies of intravenous bubble formation were undertaken.

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DEVELOPMENT OF A BENDS-SCREENING INDEX FOR AIRCREW SELECTION

INTRODUCTION

United States Air Force (USAF) aircrews must be prepared to encounter loss of cabin pressure caused by either mechanical failure or deliberate maneuvering of aircraft. Aircrews generally tolerate short-duration depressurization well, but decompression sickness (DCS) occurs much more often than is reported. Symptoms of DCS range in severity from minor to life threatening; however, all incidences of DCS require medical attention to preclude subsequent problems (3).

The physiological mechanisms involved in DCS are not completely understood, but DCS is considered to result from supersaturation of body tissues with nitrogen (N_2). Supersaturation sets in as the ambient pressure (hence the absolute pressure of N_2) decreases. Nitrogen is less soluble in blood than in tissues so that the rate of decrease of partial pressure of N_2 in tissues lags behind the rate of decrease in atmospheric N_2 pressure, resulting in formation of N_2 bubbles in blood and tissues. The tendency for bubbles to form is greater as the difference between the two pressures increases. The bubble formations may grow in size and be carried by the circulation to other parts of the body where they produce the symptoms described in Table 1 (2).

Treatment of DCS involves immediate recompression (descent to ground level), administration of 100% oxygen (O_2), keeping the subject warm and still, and hyperbaric treatment for more severe cases. Prebreathing 100% O_2 for at least 30 min before decompression produces partial denitrogenation of body tissues, thus reducing the risk of developing DCS.

A number of predisposing factors (i.e., factors which appear to place an individual at increased risk of developing DCS) have been cited (2). These factors include:

- Ill health
- Drugs, alcohol
- Exercise
- Hypothermia, hypoxia
- Age
- Obesity
- Previous exposure to decompression
- Apparent individual susceptibility

The last factor has been observed empirically, but the basis for such individual differences in susceptibility is not presently understood. The USAF School of Aerospace Medicine (USAFSAM), Crew Technology Division, Space Applications Laboratory, conducted studies aimed at identifying susceptible individuals. Technology Incorporated provided assistance and support in this research.

TABLE 1. MANIFESTATIONS OF DECOMPRESSION SICKNESS

DCS symptom	Location	Description
Bends	Joint (knee, shoulder, elbow, wrist)	Mild ache, made worse by movement, progressing to severe pain radiating along affected limb.
Creeps	Skin	Formication, paresthesiae, possibly accompanied by localized rashes, urticaria, and mottling.
Chokes	Respiratory system	Feelings of chest constriction and retrosternal pain associated with coughing.
Staggers	Nervous system	Anesthesia, paralysis, convulsions, visual disturbances, anxiety, reduced levels of consciousness, shock.

From: Harding, Richard M. and F. John. Mills. Problems of altitude. II: Decompression sickness and other effects of pressure changes. Br Med J 286:1498-1500 (1983).

The underlying mechanisms through which in vivo formation of gas bubbles results in clinical symptoms of DCS have not been determined, but complex interactions between a number of biophysical, biochemical, and physiological factors appear to be involved. To understand, and to ultimately predict, individual susceptibility to DCS, we decided to attempt to define a physiological profile of a bends-susceptible individual. This profile could be used to develop a Screening Index which would provide a method for weighting individual factors.

An extensive data base of relevant biological measurements and correlative observations of DCS is required. Physiological and biochemical measurements have been obtained from human subjects exposed to hypobaric environments under carefully controlled conditions by USAFSAM investigators; and data resulting from these studies are stored in a computerized hypobaric DCS database.

This report describes the initial study: the development and preliminary validation of a Bends-Screening Index designed to provide a rapid, noninvasive method whereby bends-susceptible individuals could be identified in the potential aircrew/astronaut population.

OBJECTIVES

Development and initial validation of a Bends-Screening Index were the overall objectives of this study. This index is composed of selected parameters demonstrated or considered to be associated with susceptibility to DCS. Parameters included were: time and degree of intravenous bubble formation under relevant aircrew stress conditions; percent body fat; age; blood values of white blood cells (WBC), red blood cells (RBC, erythrocytes), platelets, hematocrit (HCT), hemoglobin (Hgb) content, mean cell volume (MCV), and salicylate levels. Development phases of this study included setting up experimental apparatus and equipment for measuring the selected parameters, and training of subjects. A separate research phase involved investigations of in vitro DCS model systems. Validation phases included obtaining measurements from human subjects under relevant stress conditions, and storage, correlation, and analysis of data obtained.

Specific objectives of this task included: education of decompression chamber subjects; collection of data from each chamber experimental session (e.g., intravascular bubbles, DCS symptoms, and hematological data); engineering modification and maintenance of decompression chamber; providing a Physiological Training Officer and Medical Monitor for all chamber flights; development of a system to replace neck seals on the "French" masks used in experimental studies; design of an oxygen-nitrogen manifold system and exercise station mountings; installation and validation of equipment for hematological assays; collection and assay of serial blood samples from chamber subjects; and entry of these data into the USAFSAM Data Repository. After these objectives were accomplished a series of experimental studies with human subjects were undertaken and two of these studies are described in detail in this report. Another objective of this task was the study of bubble formation dynamics using relevant in vitro systems; these studies are described herein.

METHODS

Data resulting from the human subject DCS studies were entered and stored in a computerized hypobaric DCS database. Other methods used in this phase of the research are described as appropriate in the Results section.

RESULTS

Education of Decompression Chamber Subjects

Initial safety briefings were conducted with all chamber subjects concerning the mechanical effects of trapped gases and symptoms of decompression sickness. The instructions on proper descending procedures from altitude in the lock portion of the chamber were given to all chamber subjects. Subjects

were also briefed on operation of the Intertechnique ("French") neck-seal respirator and use of all ancillary portable oxygen assemblies.

Safety Monitoring of Chamber Subjects

A Physiological Training Officer and a Medical Monitor were provided for all chamber "flights." The Physiological Training Officer was responsible for all phases of chamber operations (e.g., accurate maintenance of simulated altitudes, rapid descent of chamber when required, and proper lock-out procedures). The Medical Monitor was responsible for the safety of all inside observers and experimental subjects. He also performed a brief physical examination of each subject prior to all chamber "flights."

Chamber Modifications and Engineering Maintenance

The chamber modifications that were accomplished included: (1) setting up an efficient cooling system for "C" chamber; (2) setting up a mass spectrometer to measure oxygen concentration at altitude; (3) advising on ventilation requirements for the chamber; (4) maintaining all Doppler units, masks and ECG preamplifiers; and (5) performing system checks before each chamber flight.

Oxygen-nitrogen Manifold System

An oxygen-nitrogen manifold system was designed for a zero-prebreathe experimental study. These systems were installed in both "C" and "E" chambers, along with exercise station mountings for both chambers.

Hematological Studies

Equipment for hematological analyses was installed and put into operation. This equipment included: (1) Coulter $M_4$30 semiautomated whole-blood hematology analyzer; (2) Coulter $P_2$60 whole-blood platelet analyzer; (3) Coulter dual-blood diluter model III; (4) Coulter blood mixing rocker tray; and (5) Coulter $M_4$30 computer and printer.

Serial blood samples were collected from volunteer subjects participating in experimental studies undertaken in cooperation with USAF scientists. Blood samples were analyzed for numbers of WBC, RBC, and platelets; HCT; Hgb content; MCV; and salicylate levels by the qualitative calorimetric method. Results of these measurements were entered into the USAFSAM Computer Data Repository. Data resulting from two experimental studies were further analyzed and are described in the following section.

DISCUSSION

The chamber modifications and equipment which have been installed and tested in "C" chamber at USAFSAM provide an excellent laboratory for the conduct of research into the etiology of DCS and associated problems such as optimal pressure-suit pressure or methods for evaluation of bends-prone and bends-resistant aircrew personnel. The equipment and instrumentation installed in this laboratory include breathing-gas manifolds, exercise stations, and a range of physiological monitoring equipment.

In addition to setting up the laboratory facilities, support services for physiological training of volunteer subjects participating in DCS-related experiments, medical monitoring of subjects during experiments, chamber engineering maintenance, and maintenance of the USAFSAM DCS computerized data base have been provided.

Provision of the technical and research support services described has enabled the conduct of continuing research studies aimed at relating the onset of DCS to combinations of physiological and biochemical factors. Two such studies were supported by Technology Incorporated personnel within the scope of this contract. One study used a 7.8 psia suit pressure environment and found no correlation between either body fat content or age and the incidence of bubble formation. The study also indicated that 7.8 psia was not sufficient pressure to totally preclude DCS in the 50% O_2 - 50% N_2 environment used. The second study sought to determine a minimum "bends-free" suit pressure without prebreathing 100% O_2; initial results suggested that this pressure is approximately 9.5 psia. Both studies are described in detail herein.

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INTRAVENOUS BUBBLE FORMATION USING A 7.8 PSIA SIMULATED-PRESSURE SUIT ENVIRONMENT

INTRODUCTION

This study was undertaken to determine the minimum space-suit pressure required to prevent DCS during operation in an environment of 50% oxygen - 50% nitrogen. Experimental conditions were selected to emulate extravehicular activity (EVA) conditions and safety requirements in a space shuttle.

METHODS

Detection of Intravenous Bubble Formation

During exposure, subjects were monitored for venous gas bubbles using a precordial ultrasonic Doppler technique (15). This technique uses a 5-mHz continuous-wave (CW) transcutaneous sensor to detect bubbles in venous blood as it enters the right ventricle (12). The occurrence of bubbles at higher altitudes has been shown to correlate with the subsequent development of DCS (bends). This technique has been further refined at the USAFSAM to include slow joint flexion to increase sensitivity and allow for predictability of the specific limb in which bends will occur.

Gas bubbles were graded by the method of Neuman et al. (10) as follows: Grade 0, no bubbles; Grade 1, an occasional bubble signal, with majority of cardiac cycles being bubble free; Grade 2, bubbles in many, but less than one-half cardiac cycles; Grade 3, bubbles in all cardiac cycles; and Grade 4, numerous bubbles that obscure heart sounds. Grades 1 and 2 bubbling were classified as "not severe," and Grades 3 and 4 were classified as "severe." These Doppler bubble signals were subjectively graded by a panel of experienced Technology Incorporated personnel and recorded on magnetic tape for postflight validation.

Experimental Protocol

During each altitude exposure, subjects accomplished exercise workloads that were similar qualitatively and quantitatively to light workloads anticipated during actual EVA (16). Exercise workloads consisted of a different activity at each of the 3 work stations, and were designed to emphasize upper body stress. All exercise was performed in synchrony with a 5-s audible signal transmitted to headsets worn by the subjects who rotated sequentially from 1 work station to another work station every 4 min. The subject at station 1 operated a cycle ergometer set at 0.5 kp at the rate of 2 revolutions/5 s, simulating manual closing of the shuttle bay doors. At station 2, the seated subject operated a torque wrench at the rate of one tightening movement/5 s, to simulate operational tool use during EVA. The subject at station 3 pulled a Mini-Gym rope at a resistance of 7.7 kg with alternating hands, simulating translation along a cable in the shuttle bay. A 4th (nonexercise) station was used to monitor supine subjects for venous gas bubbles.

Upon completion of each 1-h period the subjects took a 4-min rest period. A 30-min rest period was also taken at the completion of the first 3-h period.

During rest periods, subjects were encouraged to drink liquids such as water and fruit juices.

At altitude subjects breathed a nominal mixture of 50% oxygen - 50% nitrogen. This mixture was chosen because: (1) it ensured a normoxic condition; (2) it minimized potential problems attributable to hypobaric hyperoxia (6, 8, 9, 14); (3) a "nitrogen-blanket" effect may become desirable for fire safety as suit O_2 pressure increases; (4) radiation-effects enhancement of increased PO_2 at these pressures may be worth consideration; and (5) dual-gas suit technology now appears feasible.

A full-head respirator supplied breathing gas from either a spray bar over the forehead or through an oronasal mask. This specific respirator was chosen for fit and comfort during long exposures to altitude and for low risk of inboard N_2 leakage. This system provided a drinking port used by subjects to take liquids during rest periods.

Body fat measurements, using Allen's method (3), were made prior to subjects' initial flights.

This study used 30 volunteer male subjects, ranging in age from 20 to 41 years, with a mean age of 29.8 $\pm$ 4.72 SD. All subjects had passed a USAF Flying Class II physical examination and were certified in accordance with applicable USAF regulations to participate in research altitude chamber flights.

All subjects were exposed, in groups of 3, to 3 consecutive daily EVA workload simulations at a pressure of 7.8 psia for a continuous 6-h period. This pressure is equivalent to an altitude of 16,500 ft; reports in the literature indicate that the onset of DCS is rare below 18,000 ft (5, 13).

RESULTS

If a subject developed DCS symptoms on days 1 or 2, he was eliminated from further exposure. Any subject complaining of DCS symptoms was immediately returned to ground level and appropriate treatment was administered.

One subject (#22) experienced pain in the right elbow on day 1, and the pain was relieved during return to ground-level pressure. The subject was considered to have had DCS, and was eliminated from further exposures in accordance with the experimental protocol. Thus, under the conditions of this experiment, 1 of 30 subjects (3.3%) experienced DCS. Some statistics in the remainder of this paper will exclude subject 22 because of the lack of data on days 2 and 3.

Bubble pattern data are shown in Table 2. Subjects were grouped according to the frequency of occurrence of bubbling: Group A subjects did not bubble; Group B subjects bubbled on 1 d only; Group C subjects bubbled on 2 d; and Group D subjects bubbled on all 3 d. During the entire study, 26.7% (8) subjects remained bubble free, while 73.3% (22) exhibited at least Grade 1 bubbling on 1 d.

TABLE 2. SUMMARY OF BUBBLE FORMATION AT 7.8 PSIA

Group	Subject	Age	Maximum bubble grade Day 1	Day 2	Day 3	Group grade level ($\bar{X}$+SE)	Site of maximum bubble grade Day 1	Day 2	Day 3	Body fat (F/M%)	Group body fat ($\bar{X}$+SE)
A	5	33	0	0	0		-	-	-	22.6	
	8	20	0	0	0		-	-	-	14.5	
	13	27	0	0	0		-	-	-	13.1	
	16	24	0	0	0	0.0	-	-	-	23.9	20.7 ± 2.55
	21	31	0	0	0		-	-	-	35.5	
	23	23	0	0	0		-	-	-	16.4	
	25	23	0	0	0		-	-	-	22.5	
	30	27	0	0	0		-	-	-	17.2	
	$\bar{X}$	26 ± 4.38									
B	3	28	0	0	1		-	-	RL	19.1	
	6	27	0	0	3		-	-	RL	22.8	
	10	29	0	1	0	0.73 ± 0.33	-	LL	-	19.8	22.3 ± 1.21
	18	31	4	0	0		RL	-	-	24.5	
	24	38	2	0	0		RL	-	-	25.1	
	$\bar{X}$	30.6 ± 4.39									
C	4	33	0	4	3		-	BL	BL	21.3	
	7	32	2	3	0		LL	RA	-	21.3	
	9	31	3	0	1		BL	-	LL	27.0	
	19	29	3	0	4	1.81 ± 0.34	RL	-	RL	20.6	23.0 ± 1.13
	26	34	0	4	3		-	LL	LL	27.6	
	27	25	2	0	1		BA	-	RA	22.4	
	28	41	3	0	2		LL	-	LL	20.8	
	$\bar{X}$	32.1 ± 4.91									
D	1	33	4	4	4		RL	RL	BL	15.9	
	2	38	4	2	3		RL	RL	RL	25.1	
	11	27	3	2	4		BL	RL	RL	22.3	
	12	26	1	3	2		RL	RL	RA	25.9	
	14	31	4	2	4		RL	RA	RL	16.5	
	15	32	1	4	3	3.11 ± 0.18	LA	LL	LL	18.5	20.6 ± 1.17
	17	31	4	4	4		LL	BL	BL	19.5	
	20	27	3	3	3		RA	RL	RA	18.7	
	29	29	3	3	3		RL	RL	AL	20.0	
	*22	34	3	*	*		BA	-	-	23.6	
	$\bar{X}$	30.8 ± 3.71									

RL=Right Leg; LL=Left Leg; RA=Right Arm; LA=Left Arm; AL=All Limbs; BL=Both Legs; BA=Both Arms.

* Subject developed DCS on day 1 and was eliminated from further exposure.

The percentages of occurrence of bubbling on more than 1 d among those subjects who bubbled were calculated using a subject population of 29, since 1 subject developed DCS on the 1st day and was eliminated from further exposure. Thus, 16 subjects (55.2%) bubbled on at least 2 d, and 9 subjects (31.0%) bubbled on all 3 d.

There appeared to be no clear-cut relationship between bubble site and day of exposure. The most frequent site of maximum bubbles was the lower limbs, predominantly on the right side. Despite the emphasis on upper body exercise, 95.2% of those subjects who bubbled did so in their lower limbs on at least one occasion.

The majority (81.8%) of subjects who bubbled exhibited severe bubbling (Grades 3 and 4) on at least 1 d. Two subjects (40%) in Group B had severe bubbling, while 86% of Group C and 100% of Group D exhibited the higher grade levels.

No systematic interday pattern was observed for either the incidence or severity of bubbling. In Group B, 40% of subjects bubbled on days 1 and 3, and 20% bubbled on day 2. In Group C, 71% of subjects bubbled on day 1, 43% bubbled on day 2, and 86% bubbled on day 3. The severity of bubbling did not appear to differ for any one of the 3 d in any group. In Group D, for example, the mean $\pm$ SEM severity for days 1, 2, and 3 was 3.0 $\pm$ 0.39, 3.0 $\pm$ 0.27, and 3.3 $\pm$ 0.22, respectively.

No relationship was observed between percent body fat and either incidence or grade of bubble formation. This lack of relationship was supported by the nonsignificance of regression coefficients associated with percent body fat in logistic regression. For subjects who bubbled, there was also no statistically significant difference between body fat means of those experiencing severe bubbling (N=17) and those experiencing nonsevere or no bubbling (N=12); the t statistic = 0.23 ($p > .8$). In addition, the mean percent body fat for Group A (Table 2, nonbubblers) was not significantly different from the same measure for Groups B, C, and D (Table 2, bubblers), indicating no relationship between body fat and incidence of bubbling ($t = 0.53$).

Table 3 shows that the mean onset time for those subjects who bubbled (Group D) tended to decrease on successive days of exposure. The mean onset times were generally shorter for subjects who bubbled on all 3 d (Group D) compared to subjects who bubbled on 1 or 2 d (Groups B and C). However, onset time does not appear to be related to maximum grade of bubbling (Table 4).

Intraday bubbling grade patterns occurred which were characterized as "progression" or "regression." If bubble grade increased to the termination of the flight or leveled off, the pattern was designated "progression." Conversely, if bubble grade reached a maximum level and then decreased, the pattern was designated "regression." The incidence and distribution of these patterns are summarized in Table 5. The most prevalent pattern was one of "regression." This pattern was essentially constant throughout the study.

Although no correlation was found between age and incidence of any bubble formation, the mean age of the subgroup classified as exhibiting "severe" bubbling on at least 1 d was significantly higher ($p<0.02$) than the mean age of the subjects exhibiting "nonsevere" bubbling on all 3 d (Table 6).

TABLE 3. MEAN ONSET TIME OF BUBBLING
(Hours (± SD))

Group	N	Day 1	2	3
A	8	- (0)	- (0)	- (0)
B	5	2.58(0.31) (2)	2.90(0.0) (1)	1.23(0.31) (2)
C	7	1.58(1.27) (5)	2.50(2.10) (3)	2.27(0.89) (6)
D	9	1.79(0.91) (9)	1.41(0.48) (9)	1.19(0.29) (9)

Number of cases observed shown in lower parentheses.

TABLE 4. MEAN ONSET TIME OF BUBBLING GROUPED BY SEVERITY
(Hours (± SD); Number of cases in lower parentheses)

Group	N	Day 1		2		3	
		Severe[a]	Not[b] Severe	Severe	Not Severe	Severe	Not Severe
A	8	----- (0)	----- (0)	----- (0)	----- (0)	----- (0)	----- (0)
B	5	2.80 (1)	2.37 (1)	----- (0)	2.90 (1)	1.02 (1)	1.45 (1)
C	7	2.58(1.29) (4)	1.48 (1)	2.50(2.10) (3)	----- (0)	2.24(0.99) (5)	2.40 (1)
D	9	1.79(0.91) (9)	----- (0)	1.41(0.48) (9)	----- (0)	1.19(0.29) (9)	----- (0)

[a] Severe = Grades 3 or 4

[b] Not severe = Grades 1 or 2

TABLE 5. FREQUENCY OF REGRESSION AND PROGRESSION PATTERNS IN BUBBLE GRADES

Pattern	Number of subjects			Total
	Day 1	Day 2	Day 3	
Regression	11	11	13	25
Progression	4*	2	4	10
No pattern	2	0	0	2
No bubbles detected	13	16	12	41

* Includes one subject who developed DCS.

TABLE 6. MEAN AGE, FREQUENCY, AND SEVERITY OF BUBBLE FORMATION (Number of cases in lower parentheses)

Frequency[a] N days	Not severe[b] $\bar{X}$ Age (± SD)	Severe[b] $\bar{X}$ Age (± SD)	Whole group (N=29)
0	26.00 (4.38) (8)	----- (0)	26.00 (4.38) (8)
1	31.00 (4.36) (3)	29.00 (2.83) (2)	30.20 (3.56) (5)
2	25.00 (1)	33.33 (4.13) (6)	32.14 (4.91) (7)
3	----- (0)	30.44 (3.74) (9)	30.44 (3.74) (9)
Totals:	27.17 (4.59) (12)	31.29 (3.93) (17)	29.59 (4.62) (29)

[a] Number of days out of 3 days on which bubbles were detected in a given subject.

[b] Not severe = Grades 0, 1, and 2; Severe = Grades 3 and 4.

DISCUSSION

Previous studies have shown a correlation between the occurrence of DCS and the presence of intravascular bubbles (2, 4, 7). These studies, however, were conducted at pressures much lower than 7.8 psia. We had difficulty in establishing, in this study, any clear relationship predictive of clinical DCS from bubbling patterns, although it may be significant that the single case of DCS had the earliest bubble-onset time of any subject.

Some interesting trends were revealed after reviewing the bubble patterns. Successive exposures did not result in more severe bubbling nor in the occurrence of DCS. The only progressive bubbling change was a significant reduction in the time of onset of bubbling, suggesting that either bubbles or bubble precursors remained between exposures.

Results of this study indicate that a one-time exposure of 30 subjects to the conditions used here would result in a 3.3% incidence of DCS (1 of 30 subjects). Using a 95% confidence interval places the probability of DCS occurrence between 0.1% and 17.2%. Thus the minimum suit pressure that will give complete protection from DCS in a 50% O_2 environment must be greater than 7.8 psia. Presently, a reasonable approach to minimizing the risk of DCS under all conditions is to increase the exposure pressure to prevent detectable bubbling. Future studies will seek to determine this bubble threshold pressure.

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MINIMUM PRESSURE FOR A ZERO-PREBREATHE PRESSURE SUIT

INTRODUCTION

There are currently two concepts for prevention of bends during space flight EVA, without prebreathing 100% oxygen (O_2). One approach proposes low differential, staged decompression schedules in the transfer vehicle, space station, and space suit. The other approach involves the use of higher pressures in the suit, thus permitting EVA from a 14.7 psia space station without prebreathing O_2.

This study was designed to determine the minimum space-suit pressure which will prevent bends without the necessity for prebreathing before an EVA scenario. This study was a follow-on to a previous study which showed that a pressure of 7.8 psia did not totally preclude development of bends.

Earlier studies at altitudes of 25,000 ft (5.5 psia) and above have shown a correlation between the occurrence of venous gas bubbles and bends (1-3); therefore, these parameters were selected for study.

METHODS

Bubble threshold pressures were determined for 16 healthy, volunteer male subjects, 25 - 42 years of age ($\bar{X}$ = 30). All subjects were initially decompressed to a pressure of 7.8 psia (9 subjects) or 8 psia (7 subjects) in a hypobaric chamber for a maximum duration of 6 h. An Intertechnique neck-seal respirator was used to provide a 50% O_2 - 50% N_2 breathing mixture to prevent hypoxia. Workloads for EVA were simulated using 3 work stations at which subjects sequentially: (1) handturned a modified bicycle ergometer; (2) operated a torque wrench; and (3) pulled on a Mini-Gym rope.

A 4th station was used to detect intravenous bubbling using an ultrasonic precordial Doppler detector (4). Bubbling was graded in accordance with a system described by Neuman et al. (5): Grade 0, no bubbles; Grade 1, an occasional bubble signal with majority of cardiac cycles free of bubbles; Grade 2, bubbles in less than one-half cardiac cycles; Grade 3, bubbles in all cardiac cycles; and Grade 4, numerous bubbles that obscured heart sounds. Grades 1 and 2 bubbling were classified as nonsevere; Grades 3 and 4 bubbling were classified as severe.

After a subject had bubbled at 7.8/8.0 psia, he was subsequently exposed (after an interval of several days) to 9.0 psia, and, if he did not bubble at this pressure, he was retested at 8.5 psia. Thus, by increasing pressure in increments of 1 psia for those subjects who continued to bubble, and then reducing pressure by 0.5 psia when bubbling ceased, the bubble threshold was determined.

Intermittent, mild to moderate pain was classified as Grade I bends; constant muscle or joint pain was classified as Grade II bends and was the predetermined bends grade for exposure termination. Any other constant symptoms of DCS also resulted in exposure termination.

RESULTS

Bubbling which occurred at 7.8/8.0 psia ranged in intensity from Grade 2 to Grade 4 (Table 7). Severe bubbling was still present in 4 subjects at pressures up to, and including 9.0 psia. One incident of nonsevere bubbling occurred at 9.5 psia, and two cases of nonsevere bubbling were seen at 10.0 psia.

Symptoms observed are shown in Table 8. Grade II bends (constant joint pain) occurred in one subject at 7.8 psia; and Grade I bends (intermittent joint pain) occurred in one subject at 9.0 psia (Table 8). One incident of constant hot and cold skin sensations was reported which was preceded by Grade 1 bubbling. This case is shown as skin bends although the possibility of anxiety-induced hyperventilation cannot be discounted. All limbs-bends symptoms were preceded by severe bubbling, and all DCS symptoms were relieved during return to ground-level pressure.

DISCUSSION

The theoretical assumption that pressure must be halved before intravenous bubbling occurs was not confirmed by the results of this study, since Grade 1 bubbling was detected in 2 subjects at a pressure of 10 psia (a decompression ratio of 1.5) and severe bubbling occurred in 4 subjects at 9 psia (decompression ratio of 1.6).

Since previous studies at lower pressures have shown a good correlation between severe bubbling and the occurrence of bends (1-3), venous bubbling was monitored during this study. Results showed that severe bubbling occurred in 13 of 16 subjects who bubbled (81%) at pressures between 7.8 and 9.0 psia, but limb bends occurred in only 2 of the 13 subjects (15%). A much better correlation has been found in previous studies conducted at altitudes between 25,000 ft (5.5 psia) and 33,000 ft (3.8 psia) where severe venous bubbling was followed by bends in 70-100% of the cases (1-3). Nevertheless, even if venous bubble detection produced many false positives (i.e., severe bubbling without bends) it is still important to note that all limb-bends cases were preceded by severe bubbling.

We conducted this study with subjects who were thoroughly trained to recognize all symptoms. We also instructed the subjects to report the symptoms no matter how insignificant they appeared to be.

Results showed that all subjects were asymptomatic at 9.5 psia and indicated that, within the scope of this study, this pressure will eliminate the necessity of prebreathing 100% O_2 prior to EVA from a 14.7 psia station.

TABLE 7. BUBBLE THRESHOLD MATRIX
(Pressures in psia)

Subject	(7.8-8.0)	8.5	9.0	9.5	10.0	10.5
JRA	4	---	3	2	0	---
MJB	2	0	0	---	---	---
TE	3	---	0	0	0	---
JE	4	---	3	---	1	0
CAF	4	---	3	0	0	---
DNG	3	---	3	---	2	0
LG	3	0	0	---	---	---
LLH	3	0	1	---	---	---
CEJ	3	0	0	---	---	---
JMK	3	---	2	0	0	---
JCL	4	4	0	---	---	---
TEM	2	1	0	0	0	---
JWM	3	0	0	---	---	---
RP	2	---	1	---	---	---
WWR	3	0	0	---	---	---
EAV	3	1	0	---	---	---

TABLE 8. SUMMARY OF SYMPTOMS REPORTED

Subject	Psia	Symptom	Location	Maximum bubble grade	DCS grade
RP	9.0	Hot & cold sensations	Entire body	1	Skin bends?
DNG	8.0	Joint awareness	Left ankle & knee	3	-----
DNG	9.0	Intermittent joint pain	Right elbow	3	Grade I limb bends
JMK	7.8	Constant, moderate joint pain	Left & right elbows	3	Grade II limb bends

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IN VITRO OBSERVATIONS RELATIVE TO BUBBLE FORMATION IN DECOMPRESSION SICKNESS

INTRODUCTION

Decompression sickness is considered to be caused by formation of nitrogen bubbles in the body. This bubble theory explains many of the characteristics of DCS, and further support of this theory comes from use of ultrasonic equipment that detects signals in the circulation of decompressed subjects which are similar to signals produced by bubbles. Although the bubble theory is attractive, it leaves some questions unanswered. This theory does not explain, for example, why joint pains are the overwhelmingly predominant symptom, or why no symptoms occur, in some instances, at low altitudes--even when bubbles can be detected ultrasonically. Questions such as these suggest the need for studies concerning the dynamics of bubble formation.

Recent studies have contributed several concepts which are now used in DCS mechanisms research. One concept is that of "critical size" (1). Those bubbles above the critical size will grow larger while those less than the critical size will shrink and disappear. This observation appears to apply only to bubbles in a size range visible to the naked eye. We have observed bubbles in the microscopic size range, especially those in the order of a few micrometers, which have maintained their size for at least 5 min.

A second concept is the varying permeability membrane (VPM) theory which postulates that when bubbles are very small their membranes (skins) become impermeable to gas molecules. These two concepts are thought to explain why bubbles in the microscopic size range are very stable.

A third concept, the bubble nuclei concept, proposes that fluids contain bubble precursors (or nuclei) which constitute a matrix from which bubbles can grow. For example, if a sample of gas-saturated fluid containing bubble precursors were enclosed in a pressure vessel containing a piston and large mechanical pressures were applied to the piston, the fluid would become resistant to bubbling even when subsequently subjected to very low ambient pressures. The fluid behaves as if particulate gas-phase bubble precursors had been ruptured and returned to solution-phase gas (2).

A fourth and final concept is that of tribonucleation as a method of bubble formation. If a steel ball is allowed to roll down the side of a fluid-filled, inclined tube, a trail of bubbles will be left behind the ball. Shearing stress, or separation of streamlines, or separation of fluid layers, causes bubble formation (or at least bubble nuclei formation). (Also called cavitation, especially in reference to propeller effects).

Surprisingly, little is known about the biophysics and pathology of DCS; however, some general principles can be learned from experiences of subjects exposed to altitude. For example, the occurrence of bends during denitrogenation by breathing 100% O_2 at ground level is unheard of. Yet compared to the gas (O_2) the subject breathes, his body is supersaturated with N_2. From these observations supersaturation with N_2 is apparently not enough to produce bends, but it must be accompanied by a lowered hydrostatic pressure.

Because of impressive evidence in the literature of the association of DCS with bubbles (3), this study undertook to investigate dynamics of bubble formation in vitro.

METHODS

Separation of Bubbles from Gas-liquid Solutions

Two methods were used to produce supersaturated solutions with lowered hydrostatic pressures: (1) temperature effects, and (2) pressure effects.

Temperature Technique

An apparatus was designed and fabricated to produce supersaturated solutions with lowered hydrostatic pressures by temperature manipulation. A cylindrical column 1.27 cm (0.5 in.) in diameter was drilled in a Plexiglas rectangular solid, 2.54 cm x 2.54 cm x 9.525 cm (1 in. x 1 in. x 3.75 in.). This column chamber tapered to an opening 0.9525 cm (0.375 in.) in diameter at each end of the plastic. There is one other connection between the cylindrical chamber and the outside; this connection is a 0.15875 cm (0.0625 in.) capillary running at a right angle from one of the tapered ends of the chamber to the outside.

In operation, the cylinder is partly filled with fluid to be tested and the holes at the end of the apparatus are sealed with tape. The apparatus is cooled in a refrigerator; the cylinder is shaken to be sure that the fluid is saturated with air, then it is completely filled with fluid; the holes at the ends of the apparatus are taped, and the system is allowed to warm. Preliminary experiments showed that as the plastic warms, it expands so that the chamber in the center of the apparatus gains volume. This effect is demonstrated by the fact that if the capillary is left untaped as the apparatus warms up, the capillary which was initially filled with fluid gradually becomes filled with air and the fluid level in it gradually sinks as fluid runs into the expanding chamber. As the heat penetrates through the plastic and warms the fluid, the fluid begins to bubble and expand and the level of fluid in the capillary rises. As time progresses, the fluid in the apparatus which is saturated at the beginning of the experiment, becomes supersaturated as it warms up. The fluid is also subjected to the negative pressure caused by expansion of the plastic.

Pressure Technique

The second method used to produce supersaturation and decreased hydrostatic pressure is to take the sample to a simulated altitude in an experimental altitude chamber. Although this method is ideal in the sense that it is a replication of what happens to decompressed subjects, it has the disadvantage that the sample of fluid cannot be thoroughly tested while it is still at altitude. To do this test would require highly sophisticated equipment, particularly if ultrasonic and microscopic studies were needed. It should be noted at this point that although these are in vitro studies, the Results section will refer to one study done on subjects after they had returned to ground level from an altitude exposure. Although only a blood sample from

these subjects was studied, these studies do perhaps shade into in vivo studies.

Examination of Supersaturated Fluids

Two methods were used to demonstrate the presence of bubble nuclei or bubble precursors in supersaturated fluids: (1) microscopic examination, and (2) flotation techniques.

Microscopic Examination Techniques

We found that oil immersion was essential to detect bubble nuclei and that lighting was very important. Rather than using substage illumination, minute bubbles or bubble nuclei are better observed with tangential illumination. Dark-field and phase microscopy should also be considered. As will be discussed in the Results section, bubbles in the size range of <1 - 10 μm are abundant in supersaturated plasma or distilled water. One might expect, therefore, that bubbles or bubble nuclei below the microscopic range exist.

Flotation Technique

Electron microscopy is not practical for wet preparations used in these studies, but a flotation method does seem to work for plasma. Specifically, if plasma is heated to 32 - 38 ^{o}C (90-100 ^{o}F), protein will precipitate in fine strands which are very close to the density of the plasma. If left undisturbed, these precipitates slowly sink to the bottom of a plasma sample. They are so close to the density of the plasma, however, that any minute bubbles or less-dense entities adhering to their surfaces will cause them to float. One can conclude that low-density particles (bubble nuclei or bubble precursors) must be present when protein precipitates begin to float.

Induction of Bubble Formation in Supersaturated Fluids

Four different techniques were used to induce bubble formation in supersaturated fluids:

Impact Shock Wave Technique

Impact, and presumably secondary, shock waves were used to induce bubble formation. For example, if the plastic container filled with supersaturated fluid is dropped on the floor, or if it is given a sharp impact by an object constrained to move only small, even minute distances (as for example an inertial nut cracker), the fluid in the chamber develops large hazy clouds which move through the otherwise transparent fluid and gradually rise to the top of the chamber. When viewed under low power of a microscope, the haze is seen to be masses of minute bubbles.

Surface Technique

Another way to produce bubbles in supersaturated fluid is simply to provide a suitable surface for them to form on and then wait. A discussion of surface material and consistency (rough vs. smooth) is beyond the scope of this paper, but is an important area of investigation. The plastic chamber

just described has 2 different surfaces: one end is rough and the other end is smooth. Bubble formation appears to be accentuated by smooth surfaces.

Streamlines Technique

Bubbles may be produced by the separation of streamlines. A bubble chamber which can be viewed under a microscope was constructed. When fluid is forced into the inlet port, it flows through the chamber following streamlines which diverge at the entrance and converge at the exit since the chamber is circular. Bubbles form at the entrance where the streamlines diverge.

Tribonucleation Technique

If a drop of fluid is placed on a microscope slide and covered with a cover slip which is moved back and forth across the slide, minute bubbles will be formed which can be seen under the microscope.

As pointed out earlier, some of the inciting techniques are potent enough to create bubbles even if the fluid is not supersaturated. The intensity of the activating force (intensity of impact or velocity of flow for streamline separation) should be adjusted accordingly.

Bubble Characterization

After producing bubbles, the final aspect of this research involved characterizing the bubbles and their interactions with the environment. Bubble size is easily determined in most cases by direct observation. Under the microscope, bubbles can be compared to objects of known size (e.g., red cells).

One area, however, which does need discussion is the possibility of measuring bubble size by the signal produced in the ultrasonic signs. Techniques for doing this measurement have been described in the literature and involve highly refined ultrasonic equipment. In these studies, we tried to determine only the smallest bubble which could be detected ultrasonically. An ultrasonic transducer was placed over the cover of a bubble chamber and ultrasonic signals were compared to the bubbles that produced the signals, and which were seen under the microscope. The smallest bubble which could be detected ultrasonically was determined. It should be noted, however, that the cover slip through which ultrasound had to pass was very thin so that little signal attenuation occurred. Results from these experiments cannot, therefore, be compared directly to human studies, where signal attenuation is much greater.

Other than size, another characteristic of bubbles is rigidity, or deformability. This characteristic could be estimated by noting how much bubbles deformed when they collided with other objects in the microscopic field such as red blood cells. Red cells and bubbles can be made to collide by moving the cover slip over a slide, as when producing tribonucleation.

Finally, a few studies were performed on the movement of bubbles through interfaces. Peanut oil was layered over plasma or distilled water, as for example in the plastic chamber previously described. When bubbles were present, their interactions with the oil-aqueous interface could be determined.

RESULTS AND DISCUSSION

This experiment began when the aforementioned cold cylinder was filled with cold saturated distilled water or plasma, and the capillary at one end of the chamber had a predetermined fluid level. As the chamber began warming up to room temperature, the plastic expanded first; the chamber became larger and was under reduced pressure since all holes in the apparatus, including the capillary opening with the fluid level, were taped. The fluid level fell at first, then became stabilized, and finally began to rise. If a sample of fluid were examined microscopically just as the fluid was beginning to expand, small (0.5 to 10 μm) spherical entities could be seen which moved vigorously under Brownian movement; there were 5 to 10 of these entities per oil immersion field. The same-appearing entities, presumably bubbles or bubble nuclei, can be seen occasionally in blood taken from subjects experiencing DCS. These entities are quite stable, persisting for hours at a stable size. It is remarkable that although the fluid must be loaded with these particles, it does not seem to occupy a volume much larger than it occupied when it was cold, at which time few or none of these entities were present. (We are still trying to confirm the absence of these entities in cold fluid.) These entities do not coalesce, and appear to be rigid as judged by their nondeforming properties when they collide with other particles such as red cells.

When the chamber is impacted and numerous minute bubbles are produced, the entities just described disappear or are greatly decreased in number, suggesting that they were the precursors of the bubbles. If, rather than using impact, the fluid is left undisturbed, a few bubbles will eventually form in the chamber, and the fluid level will rise. This process continues until the fluid level returns to its original level, indicating that the pressure in the chamber has returned to atmospheric pressure.

The plastic chamber is considered analogous to a closed tissue compartment in the body, such as a muscle or tendon surrounded by its fascia. With the drop in pressure in the compartment due to decompression, bubbles will form until the pressure in the compartment returns to its original predecompression level; bubble formation will then cease. The amount of bubbles and the resulting stretch on the limiting membranes of the tissue will be determined by the altitude (ambient pressure). At high altitudes, for example, the pressure in a closed tissue space is low, and it will take large numbers of bubbles to raise the tissue pressure back to ground level. The occurrence and degree of pain sensed will depend on the amount of stretch. If the altitude is low enough, the pressure in the compartment can be returned to ground level with few bubbles and little stretch of surrounding tissue, and consequently little or no pain is felt.

We found that bubbles in aqueous solutions penetrate oil-aqueous interfaces well, but that bubbles in oil will not enter aqueous solutions, or if they do, they carry a coating of oil with them. Also small bubbles and bubble nuclei are very hard because they can indent other particles without themselves being deformed. These observations make it unlikely that bubbles or bubble nuclei visible under the light microscope can cross biological membranes, such as capillaries. The bubbles heard ultrasonically probably arise intravascularly, and bubbles which form in the extravascular spaces presumably remain there. In conclusion, therefore, conditions which produce intravascular bubbles also produce extravascular bubbles. The smallest bubbles which

could be detected were about 100 μm. This does not necessarily mean, however, that bubbles this small could be detected in the human circulation where the separation between target bubbles and the ultrasonic transducer is much greater.

CONCLUSIONS AND FINDINGS

We emphasize the importance of the conversion of gas-supersaturated liquid solutions to bubble-laden fluid. Future research should be directed toward this phenomenon. We have alluded, for example, to the importance of the surfaces on which bubbles form. Smooth surfaces seem to be more prone to bubble formation than rough surfaces. The inciting factor for the conversion of supersaturation to bubbles seems, from these preliminary studies, to determine to some extent the size of the bubbles. For example, if the cylinder containing supersaturated fluid is struck by an impulsive force such as a nutcracker, the resulting bubbles are very small and barely visible to the naked eye. On the other hand, if the cylinder is dropped through a height of several feet, the resulting bubbles are considerably larger, clearly in the visible size range. Finally, the role of bubbles 1 μm and smaller in this conversion should also be studied. Blood from one symptomatic decompressed subject showed a multitude of bubbles in this size range in his blood, many of them coating red cells. This finding, however, has not been reproduced in other subjects as yet.

The main findings to date of these in vitro studies are:

(1) Bubbles in the range of 100 μm can be detected ultrasonically if the distance between target bubbles and transducer is negligible.

(2) Gas-supersaturated liquid solutions are quite stable, and the separation of bubbles is catalyzed by mechanical forces such as impact, cavitation, and tribonucleation (joint movement probably produces all three).

(3) Bubble formation in a closed space such as a Plexiglas cylinder ceases when the pressure in the space reaches the initial ambient pressure.

(4) Bubbles as small as 1 μm exist and are stable; they appear to be the matrix on which larger bubbles form.

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