NASA Technical Memorandum 104762

Project ARGO— Gas Phase Formation in Simulated Microgravity

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Acronyms

ASA	acetylsalicyclic acid
ASD	atrial septal defect
ATA	atmospheres absolute
CI	confidence intervals
CMB	circulating microbubbles
CNS	central nervous system
DCS	decompression sickness
DPL	dipalmitoyl lecithin
EVA	extravehicular activity
FFT	fast Fourier transform
fsw	feet of sea water
ID	identification
JSC	NASA/Lyndon B. Johnson Space Center
MCA	middle cerebral artery
PFO	patent foramen ovalae
psi	pounds per square inch
RVSP	right ventricular systolic pressure
STP	standard temperature and pressure
TCD	transcranial Doppler
TR	tissue ratio
USAF	United States Air Force

Summary

The ARGO study investigated the reduced incidence of joint pain decompression sickness (DCS) encountered in microgravity as compared with an expected incidence of joint pain DCS experienced by test subjects in Earth-based laboratories (unit gravity). Individuals who are decompressed from saturated conditions usually acquire joint pain DCS in the lower extremities if decompression is from depth to the surface or from the surface to altitude. In all NASA studies, the incidence of joint pain DCS is approximately 17% with a predominance of problems (83%) occurring in the legs (mostly the knees). This is true even if individuals exercise the upper body (e.g., rope pulling or a crank ergometer). Since walking in unit gravity is the predominant exercise, it is suspected that walking generates tissue gas micronuclei that can later expand during decompression to cause pain.

Our hypothesis is that the incidence of joint pain DCS can be limited by a significant reduction in the tissue gas micronuclei formed by stress-associated nucleation. Reductions in dynamic and kinetic stresses *in vivo* are linked to hypokinetic and adynamic conditions of individuals in zero g. Doppler ultrasound bubble detection was employed to determine quantitatively the degree of gas phase formation in the upper and lower extremities of test subjects during decompression. A crossover experimental design indicated a considerable reduction in the [time integral] Doppler bubble grade in the lower extremities of subjects in simulated microgravity (bed rest) as compared to that of ambulatory subjects in unit gravity. A *chi*-square test showed that precordial Grades III and IV differed in the two groups at the $p = 0.05$ level. From our simulated microgravity studies, we could predict a reduced incidence of DCS on orbit, although the predicted mild DCS incidence still remains larger than that encountered on orbit.

The presence of gas bubbles in arterial circulation can lead to neurologic DCS, a very grave malady that can follow decompression in deep-sea or scuba divers or in astronauts during extravehicular activity. We examined hypobaric decompression cases where the test subjects displayed evidence of a large number of small gas bubbles in the right heart—a relatively common occurrence in altitude decompressions. In two cases, Spencer Grade IV gas bubbles were detected in the right heart and the subjects displayed evidence of decompression illness (paresthesia in a dermatomal distribution in one subject, and abdominal rash and orthostatic intolerance in the other subject). A "resting" patent foramen ovalae (PFO) was found upon saline contrast echocardiography in both individuals. Another subject had a resting PFO with saline contrast and developed a Spencer precordial Grade IV, but that subject did ***not*** give evidence of arterialization upon insonation of either the middle cerebral artery or the common carotid. The reason for the absence of crossover in this individual is not known. To date, we have found no evidence of right-to-left shunting through pulmonary vasculature. The volume of gas bubbles present following decompression was examined and compared with the number of gas bubbles present following saline contrast injection, and the estimates are comparable.

Two studies that were not reported here include a study involving cardiopulmonary manifestations of large venous bubble loads (Mark Davis, M.D.) and another study involving neuropsychometric testing (K. Vasantha Kumar, M.D.).

Summary Statements

Part I:

Joint Pain and Doppler-detectable Bubbles in Altitude (Hypobaric) Decompression

1. Decompression gas phase (bubble) formation occurs most commonly (>80%) in the lower extremities of individuals who are decompressed from saturation conditions experienced both in deep-sea diving and in altitude decompression.

2. Symptoms of joint pain occur most commonly in the lower extremities of subjects in altitude decompression. The upper extremities of these subjects are usually spared unless arm exercise during decompression is very intense (e.g., push-ups).

3. Detection of circulating microbubbles by Doppler ultrasound can reasonably indicate whether the specific limb of a subject will be affected by decompression joint pain.

Part II.

Decompression In Simulated Microgravity

1. Following decompression, bed rest reduces the amount of gas bubbles detected in test subjects by Doppler ultrasound flowmeters.

2. This reduction is usually associated with a smaller incidence of joint pain (although this is not proven for 3-day bed-rested individuals).

3. DCS was detected in subjects under both test conditions (bed rest and ambulatory).

4. Quantitative indications or recommendations for changes in current NASA procedures must be made cautiously because of the limited number of test subjects and the specific test conditions of Project ARGO.

Part III.

Neurologic Decompression Sickness: Transcranial Doppler Ultrasound Monitoring During Hypobaric Decompression

1. Several bed-rested subjects produced gas bubbles in the venous return and in the right side of the heart. These subjects would be susceptible to neurologic DCS from right-to-left shunts—either cardiac or pulmonary.

2. Two out of three individuals (one ambulatory, the other bed rested) with atrial septal defects and gas bubbles developed either frank neurologic DCS or an unexpected response to decompression (viz, skin mottling and orthostatic intolerance).

3. These neurologic involvements are serious problems, and the need for recompression facilities on orbit cannot be eliminated from the ARGO study.

Part I:

Joint Pain and Doppler-Detectable Bubbles in Altitude (Hypobaric) Decompression

Summary

1. Decompression gas phase (bubble) formation occurs most commonly (>80%) in the lower extremities of individuals who are decompressed from saturation conditions experienced both in deep-sea diving and in altitude decompression.

2. Symptoms of joint pain occur most commonly in the lower extremities of subjects in altitude decompression. The upper extremities of these subjects are usually spared unless arm exercise during decompression is very intense (e.g., push-ups).

3. Detection of circulating microbubbles by Doppler ultrasound can reasonably indicate whether the specific limb of a subject will be affected by decompression joint pain.

I. Introduction

Astronauts have reported a lower incidence (0%) of decompression sickness (DCS) during extravehicular activity (EVA) than would be predicted (23% mild DCS) from canonical decompression studies performed in ground-based laboratories. We hypothesize that this anomaly can be traced to a physiologically significant reduction in tissue gas micronuclei formed by stress-assisted nucleation. We have termed this the *abaroferric hypothesis*, a term we evolved from Greek and Latin roots that means "non weight bearing."

Hypobaric decompression presents an interesting area for research in decompression physiology since questions of dissolved gas uptake are generally eliminated because all of the subjects are saturated at sea level. The focus can then be on gas phase formation and/or gas phase growth in conjunction with the usual dissolved gas elimination.

To examine the question of the "decompression risk anomaly," we can study the degree of whole-body gas phase formation noninvasively, by means of Doppler ultrasound bubble detection under conditions of simulated microgravity.

DCS can occur when individuals are subjected to a reduction in ambient pressure and when the sum of the partial pressures of dissolved inert gases in certain tissues exceeds the ambient pressure. Historically, reduction of pressure to subatmospheric was the first incidence of DCS (Boyle, 1670). Responses to decompression vary in ways that have been ascribed either to differences in gas uptake and elimination or, in the last 2 decades, to a variation in the mechanisms that form the initial gas phase in a microvolume of tissue. These questions can be studied in decompression from sea level to altitude, since only elimination of dissolved gas or of free gas formation can be implicated because all individuals begin decompression with essentially the same [saturated] gas load in all tissues.

Joint pain DCS (the "bends") occurs in movable joints. In the last several decades, kinetic activity has been implicated as playing a major role in the genesis of gas phase transitions (Harvey et al., 1944, 1951;

Blinks et al., 1951). The conclusion is that musculoskeletal motion, which is able to produce temporary reductions of pressure in localized microvolumes of tissue, assists in the creation of a void in a liquid that can be stabilized by the inward flux of dissolved gas from the surrounding fluid. This helps to explain why decompression in living creatures can effect the formation of a free gas phase at considerably smaller pressure changes than can be achieved by decompression of quiescent, gas-saturated water *in vitro*.

In the terminology of the deep-sea diver, decompression to altitude is also known as "saturation-upward excursion" diving. The tissues of virtually all individuals are saturated with air at sea level, and variations in the rate of gas uptake in differing tissue microvolumes is not a factor. Safe or uneventful decompression is then a question of

1. maximizing the rate of elimination of dissolved inert gas, and

2. preventing or minimizing gas phase formation in certain tissue types.

In the conventional Haldane interpretation of the etiology of DCS, factors one and two are closely united by the concept of "critical supersaturation," although the opposing effects of musculoskeletal activity and hydrostatic compression in many animals indicate that the two effects can often be viewed as independent.

In comparison to research involving deep-sea or scuba diving, the incidence of DCS (from "niggles" to DCS requiring recompression treatment) is relatively large in altitude chamber studies. This in part reflects a higher tolerated incidence of mild, pain-only DCS in operational procedures. For NASA EVAs, it was originally projected to be several percent (although this level has not been encountered operationally). The incidence of DCS for a given oxygen prebreathe period (to effect inert gas washout) has been determined from ground-based chamber studies that consider the operational constraints while on orbit—a rate that would be unacceptable in most commercial and peacetime military diving operations. While predicted from studies conducted under unit gravity conditions, this incidence has reportedly not been encountered during EVA on orbit. If there is a predilection for joint pain DCS to occur in the lower extremities, a reduction in activity of a subject's legs in microgravity, especially with respect to weight bearing activities, might lead to a lower incidence of joint pain DCS. In this section, we will review the sites and incidence of joint pain DCS encountered in research performed at the NASA/Johnson Space Center (JSC).

II. Data Collection Methods

The subjects of the altitude studies described were men and women who were paid volunteers and who supplied written informed consent. During altitude chamber testing of oxygen prebreathe procedures for astronauts prior to EVA, exercise is performed in an altitude chamber at a similar average level as that measured during EVA (Conkin et al., 1987). This exercise takes place at various stations where subjects perform upper body movements (for example, turning crank ergometers or pulling ropes under tension). The subjects are generally standing, and they walk the short distance from exercise station to exercise station. In all cases, the individuals were breathing oxygen in a positive pressure hood with an oronasal mask. During both EVA (under microgravity conditions) and chamber tests (under unit gravity conditions), the planned musculoskeletal exercise or activity primarily involved the subject's upper body. Data regarding Doppler-detectable gas bubbles and the sites and incidences of joint pain DCS were recorded for various studies. The majority of these studies investigated the incidence of DCS at different decompression ratios (Conkin et al., 1987).

Doppler ultrasound monitoring was performed at the precordial site (Spencer and Johanson, 1974) by trained and skilled operators using an instrument manufactured by

the Institute of Applied Physiology and Medicine, Seattle, Washington, with the signal generator (transducer crystal) driven at 2 MHz. Gas bubble signals were graded and confirmed by individuals within the group, and all of the audio signals were recorded for later study or verification when necessary.

All subjects were supine during the Doppler monitoring periods, and all performed a predetermined sequence of limb movements consisting of elevations and flexions of the right arm, right leg, left leg, and left arm. By means of this sequential method, it could be determined in which limb the vascular gas phase was spawned (Spencer and Johanson, 1974). This gas phase almost assuredly is not from the joint or its associated connective tissue but, rather, from the muscle and adipose tissue of the limb (Powell, 1972a, b; Powell and Weydig, 1974). Recorded were both limb(s) responsible for the generation of Doppler-detectable gas bubbles and the limbs that were the site of occurrence of DCS.

From these data, a retrospective analysis has been performed on the results from altitude chamber decompressions conducted at JSC over the past decade to determine both the sites of joint pain DCS and the extremities from which Doppler-detectable gas bubbles could be found during decompression. All incidences relate to decompressions at unit gravity since, to date, EVA DCS has not been reported by astronauts from either the U. S. or the Russia.

III. Results

A. Sites of Occurrence of Joint Pain DCS

A summary of all of the sites of occurrence of joint pain DCS in more than 400 individual NASA test subjects is given in table 1-I, and a graphical summary is shown in figure 1-1.

It can be seen that, of the anatomical sites for DCS incidence, the knees of test subject were the joints primarily involved. In JSC tests, altitude DCS generally presented first (73/88 = 83%) in either the ankle, knee, or hip. The intensity of the pain is not indicated here, although distinctions were made at the time of the test. In all cases of pain resulting in impairment of performance where the subject had to be removed from the test, the problem was in a lower extremity.

There was a tendency for the right of the subject to be more involved, possibly an indication of greater musculoskeletal activity. This was noted earlier by Hornberger (1971) in subjects exposed to altitude for but short durations. This predilection may be an indication of the "chaotic" nature of some events in DCS; that is, there is a sensitive dependence on initial conditions. In this case, those conditions might be a tendency to lean or to initiate walking or stair climbing on one leg, which would slightly increase the stress on that limb.

TABLE 1-I. Sites of Joint Pain DCS

Location	Number of Subjects
Left Shoulder	1
Left Elbow	3
Left Wrist	1
Left Hip	0
Left Knee	18
Left Ankle	7
Right Shoulder	1
Right Elbow	0
Right Wrist	3
Right Hip	0
Right Knee	29
Right Ankle	16
Total Number of Cases of DCS	88

B. *Sites of Occurrence of Doppler-detectable Gas Bubbles and the Relationship to DCS*

If we simply regard the presence or absence of Doppler-detectable gas bubbles as an indicator of DCS, the relationship is poor. If, however, it is recognized that more gas bubbles in some type of relative ranking might indicate an increased tendency towards DCS, the relationship is improved. This was first demonstrated with pigs (Powell, 1974) and then with human diving subjects (Powell and Johanson, 1978; Nashimoto and Gotoh, 1978). The general relationship between the Spencer Doppler Grade (without regard to localization from any limb) and the incidence of DCS is shown in figure 1-2. As was found by earlier workers in the field, it is evident that more vascular gas bubbles are associated with a higher incidence of joint pain DCS, although this does not mean that these circulating gas bubbles are responsible for the joint pain.

The limbs responsible for the generation of Doppler-detectable gas bubbles are given in table 1-II along with the site of the first occurrence and, in some cases, the second occurrence of pain during the same exposure. A summary of Doppler Grades for each limb is given in table 1-III. If we examined the risk of DCS where the Spencer Doppler Grades were II or IV, there was a considerably higher risk compared to grades equal to or less than Grade II (table 1-IV). This risk was significantly higher in the lower limbs and was independent of "tissue ratio" (TR). This ratio was calculated for the 360-minute halftime tissue and was the ratio of dissolved tissue nitrogen to the ambient (chamber) pressure (Conkin et al., 1987).

The presence of detectable gas bubbles from several sites was examined. The risk of DCS was not significantly higher if bubbles were detected in either single or multiple limbs (table 1-V).

Paradigms seen here with respect to the risk of DCS and relative numbers of precordial, Doppler-detectable gas bubbles (conventionally termed "Grades") are not necessarily those seen in dives with short bottom times (sometimes called "bounce" or "intervention" diving).

IV. Discussion

While the observation that decompression to altitude is associated with pain in the lower extremities is not new, it is not a consistent finding. Hornberger (1971) indicates cases of joint pain DCS following exposure to 12,000 m in which 3% of the cases involved the *upper* body (110 cases of DCS in 2101 individuals). These decompressions were "indoctrination flights" with a duration of only 10 minutes during which the subjects were sitting quietly. DCS in divers occurs generally in the upper body, an effect often attributed to nonloading of the body while immersed. An example of the distribution is shown in figure 1-3 (Elliott and Kindwall, 1982). In decompression from saturation, the preponderance of pain is encountered in the lower extremities (Hanson et al., 1978). These authors remark,

> Another factor which may have played a part is that, like caisson workers, the diver in the compression chamber is in a weight-bearing condition in contrast to the diver who is weightless.

Longer duration altitude exposures with the subjects sitting quietly will result in a greater percentage of individuals with pain in the lower extremities (Stewart et al., 1943). When deep knee bends are performed, the percentage of "bends" in the lower extremities increases greatly (Ferris and Engel, 1943). In caisson workers, DCS is more common in the lower extremities (Golding et al., 1960; Rose, 1962). In hypobaric exposures, the data of Ferris et al. (1943) (fig. 1-4) indicate that the lower extremities are the predominant site of pain when knee flexes are performed. When push-ups are done, the primary site of pain shifts to the upper extremities.

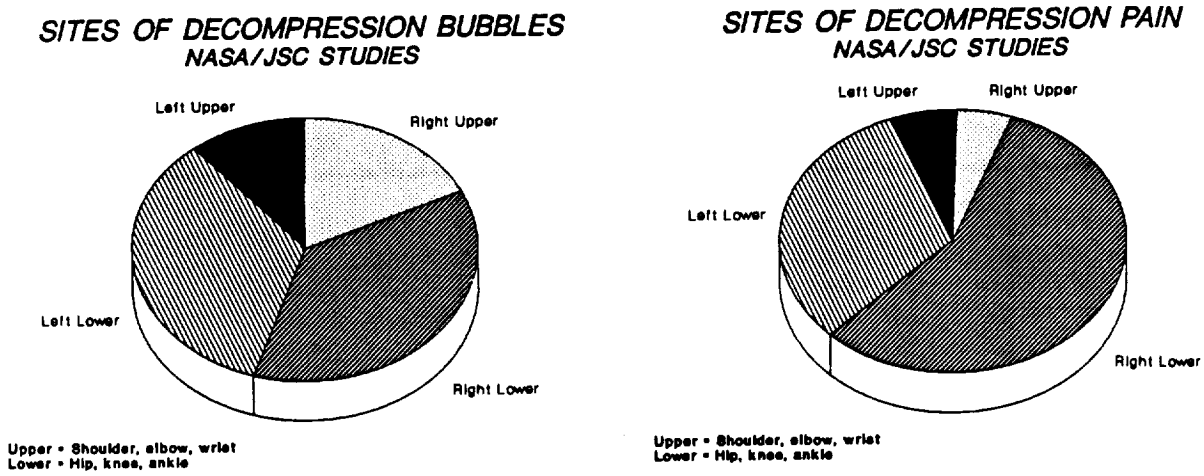


Figure 1-1. Sites of joint pain DCS.

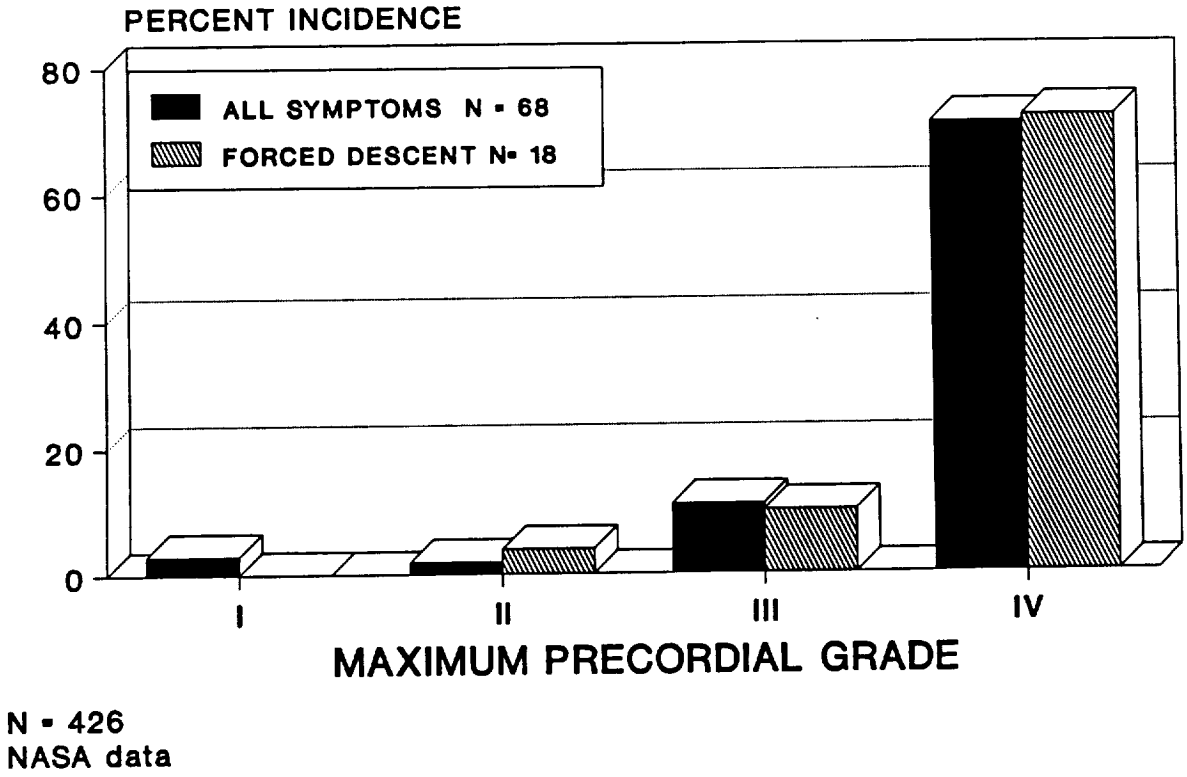


Figure 1-2. Incidence of DCS vs. Doppler grade.

Table 1-II. Sites of Occurrence of Joint Pain DCS in Simulated EVA and the Associated Maximum Spencer Doppler Grade

TEST ID	MAXIMUM SPENCER PRECORDIAL DOPPLER GRADE				JOINT PAIN SITE	
	LA	LL	RA	RL	First Pain	Second Pain
001-01	0	0	0	1	5	
002-01	0	3	0	2	11	
003-03	0	1	3	3	11	12
005-02	0	0	2	4	11	12
008-04	3	4	3	4	11	12
010-02	0	2	3	4	11	
010-07	1	3	0	0	6	
011-01	3	4	4	4	5	11
011-02	4	4	4	4	5	11
012-01	0	0	4	4	11	
013-04	1	4	1	4	5	
015-01	1	3	2	4	11	12
018-01	1	2	4	4	11	
018-02	4	4	4	4	11	
019-01	3	4	4	4	11	
020-01	3	3	4	4	11	
021-01	1	2	2	3	12	
021-02	0	4	0	3	6	
021-03	3	4	0	2	1	
025-01	3	4	4	4	6	
026-01	0	1	0	0	5	
027-01	0	0	2	2	11	
027-05	1	1	0	4	11	
031-03	0	1	0	0	12	
031-06	0	1	3	4	11	12
032-01	3	0	4	4	11	12
034-01	1	4	4	4	11	
034-02	4	4	3	4	5	11
035-02	1	3	1	4	12	
035-03	0	4	3	2	5	
037-02	2	0	1	4	11	
038-03	0	3	1	0	5	
042-02	2	2	3	4	11	
042-05	1	1	1	3	12	
044-01	0	3	3	4	12	
044-02	3	4	4	4	11	
044-03	1	1	1	2	12	12

Joint Pain Location Key

1	=	Left Shoulder	7	=	Right Shoulder
2	=	Left Elbow	8	=	Right Elbow
3	=	Left Wrist	9	=	Right Wrist
4	=	Left Hip	10	=	Right Hip
5	=	Left Knee	11	=	Right Knee
6	=	Left Ankle	12	=	Right Ankle

Table 1-II. Concluded

TEST ID	MAXIMUM SPENCER PRECORDIAL DOPPLER GRADE				JOINT PAIN SITE	
	LA	LL	RA	RL	First Pain	Second Pain
046-01	4	4	3	4	11	
047-01	0	4	0	4	5	
047-02	0	4	1	0	5	
048-03	1	3	1	3	11	
051-01	0	0	0	0	6	
060-01	1	2	3	4	9	
060-03	0	0	1	4	1	
061-03	1	4	2	3	5	
062-02	0	1	0	0	5	
063-01	3	4	2	4	12	
064-01	4	4	2	4	2	
091-01	0	2	0	4	12	
092-01	0	3	1	2	7	9
096-01	1	4	2	4	6	
097-01	2	3	3	4	11	
109-01	0	2	2	4	6	
112-01	0	1	0	0	6	
117-01	0	4	1	3	5	
120-01	1	4	1	4	5	
121-01	3	4	3	3	6	12
121-02	4	4	2	4	5	6
122-02	0	3	0	3	2	
123-01	1	4	1	4	11	
127-01	2	3	3	4	12	
133-01	0	3	3	4	11	
133-02	0	4	0	4	11	
136-01	2	4	3	4	2	
137-02	2	4	0	2	5	
138-01	0	4	1	4	11	
139-01	4	0	0	0	3	
139-02	0	0	0	0	12	
140-01	2	4	4	4	9	
140-02	2	3	2	4	9	
146-02	0	0	0	0	5	11
147-01	4	4	0	4	5	
157-01	0	0	0	9	0	
158-01	0	4	0	0	6	
164-01	0	4	0	3	5	

Joint Pain Location Key

1	=	Left Shoulder	7	=	Right Shoulder
2	=	Left Elbow	8	=	Right Elbow
3	=	Left Wrist	9	=	Right Wrist
4	=	Left Hip	10	=	Right Hip
5	=	Left Knee	11	=	Right Knee
6	=	Left Ankle	12	=	Right Ankle

Table 1-III. Distribution of Cases of DCS by Site and Maximum Spencer Doppler Grade

Site and Maximum Grade of Microbubbles	Symptoms of DCS (%)	
	Present	Absent
1. Left Arm		
Grade 1	0 -	36 (41)
2	1 (25)	27 (31)
3	1 (25)	17 (19)
4	2 (50)	8 (9)
Total	4 (100)	88 (100)
2. Left Leg		
Grade 1	3 (13)	15 (12)
2	1 (4)	26 (20)
3	2 (8)	40 (31)
4	18 (75)	48 (37)
Total	24 (100)	129 (100)
3. Right Arm		
Grade 1	1 (25)	35 (30)
2	1 (25)	30 (26)
3	1 (25)	30 (26)
4	2 (25)	21 (18)
Total	4 (100)	116 (100)
4. Right Leg		
Grade 1	0 -	18 (15)
2	3 (25)	26 (22)
3	5 (25)	29 (25)
4	30 (50)	45 (38)
Total	38 (100)	118 (100)

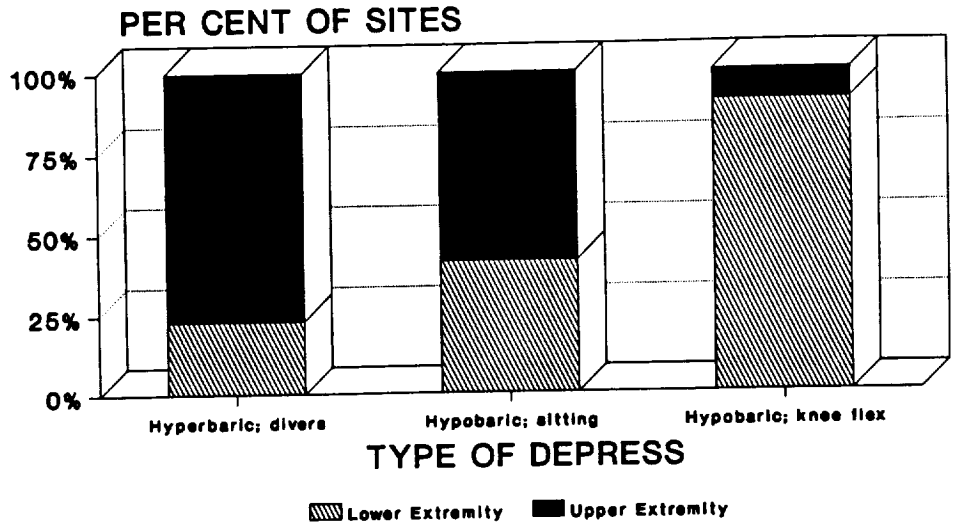
Table 1-IV. Relative Risk of Developing Bends Pain in a Limb When Circulating Microbubbles Are Detected

Microbubble Status	Bends Pain		Crude Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)	p-value
	Present	Absent			
1. LEFT ARM					
Grade <3	2	80	1.00	1.00	
>3	2	8	10.00 (0.61-148.12)	10.07 (1.42-71.43)	0.06
2. LEFT LEG					
Grade <3	6	81	1.00	1.00	0.001*
>3	18	48	5.06 (1.75-16.51)	5.70 (1.77-18.33)	
3. RIGHT ARM					
Grade <3	3	95	1.00	1.00	
>3	1	21	1.51 (0.03-19.80)	2.96 (0.34-25.84)	0.56
4. RIGHT LEG					
Grade <3	8	73	1.00	1.00	
>3	30	45	6.08 (2.43-16.56)	6.01 (2.34-15.44)	<0.001*

*p-values based on differences of Grades 0, I, II, III, and IV
+Odds ratio adjusted for 360-minute halftime tissue ratio (<1.50 and >1.50)
95% CI = 95% confidence intervals.

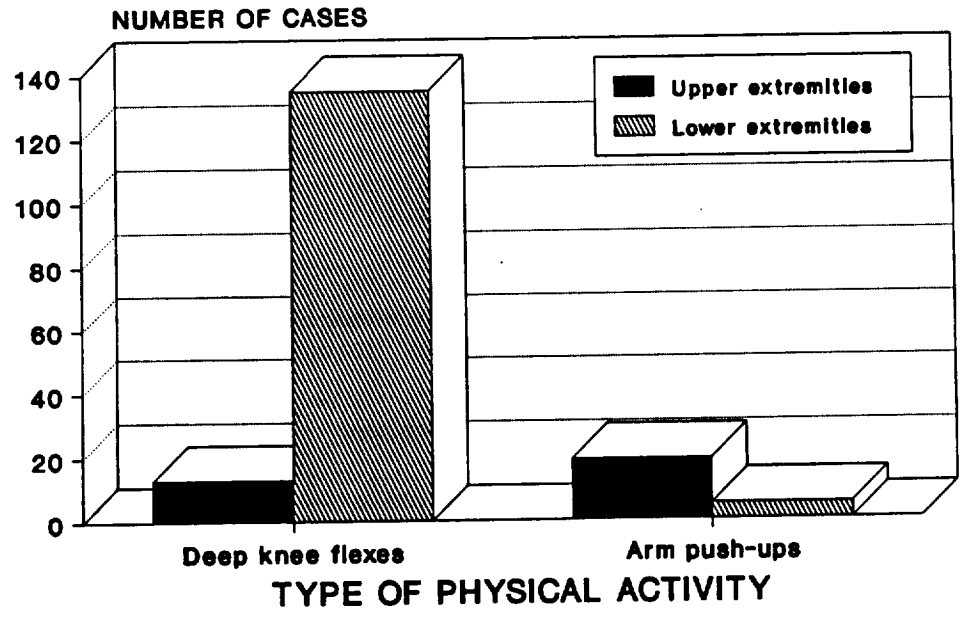
Table 1-V. Risk of DCS When Microbubbles Were Detected in One or More Limbs

MICROBUBBLES DETECTED IN	SYMPTOMS PRESENT	SYMPTOMS ABSENT	ODDS RATIO (95% CONFIDENCE INTERVAL)
1 Limb	6	16	1.00
>1 Limb	64	92	1.86 (0.65-6.09)



After Stewart et al., 1943;
Elliot and Kindwall, 1982

Figure 1-3. Sites of decompression pain distribution in those individuals with joint pain.



After Ferris et al., 1943

Figure 1-4. Sites of decompression pain (hypobaric decompression).

In a review of published reports concerning altitude DCS, many workers do not mention the location of DCS joint pain, apparently because they consider the pain to be random. This is not usually the case, however, especially for TRs encountered in studying decompression associated with simulated EVA.

A. Joint Pain in the Lower Extremities

Even when the upper body was exercised, subjects experienced a predominance of joint pain DCS in the lower extremities. We hypothesize that this pain occurs at these locations because gas nuclei are formed in tissue by kinetic and tensile forces (stress-assisted nucleation) when the subjects ambulate in a unit gravity environment. Wilhelm Ostwald, a German physical chemist who was a contemporary of John Scott Haldane, mentioned earlier that this concept of variations within microvolumes can lead to generalized phase transitions.

On Earth, lower body activity is a natural consequence of the activities of daily living. Even if lower body activity is not specifically invoked during the [typically] 3-hour decompression periods, test subjects stood during the studies from which the data for this report were obtained.

Krutz and Dixon (1987) found that pain in the lower extremities predominated with 71% (20/28) of the incidences. They comment that this is true even when the work performed during decompression was in the upper body. In another study with women as subjects, Dixon, Krutz, and Fisher (1988) observed that 88% (22/25) of the joint pain DCS cases were in the lower extremities.

B. Mechanism of Formation of the Doppler-detectable Gas Phase

Currently, three fundamentally different concepts exist involving gas phase formation in supersaturated *in vivo* systems. These are (1) the metastable state (proposed by J. S. Haldane), (2) random nucleation (Hills, 1966), and (3) stress-assisted nucleation (originally proposed by E. N. Harvey and L. R. Blinks).

The concept of the time-invariant stability of supersaturation, or the "metastable state," was first used by J. S. Haldane (Boycott, Damant, and Haldane, 1908) to calculate his decompression tables. Haldane proposes that a two-phase, gas-liquid system would not form if

$$P_{\text{dissolved inert}} < P_{\text{metastable limit}}.$$

An inert gas partial pressure P_n that falls between the metastable limit (which was a fixed partial pressure) and the saturation pressure would not separate and produce DCS. A strict interpretation of the concept (as originally envisioned by Haldane) shows the "metastable limit" is not affected by energy density fluctuations such as would be effected by mechanical motion (muscle activity). The concept of the metastable state has been largely abandoned in contemporary explanations of the pathophysiology of DCS. The formalism is employed almost universally in algorithms that calculate decompression procedures for both altitude excursions and diving, however, because it combines a relative degree of physical actuality with an easily solved algorithm.

The formation of a gas phase at a hydrophobic interface was proposed by Hills (1966). He proposes that whenever

$$P_{\text{ambient}} < P_{\text{inert}} + P_{CO2} + P_{O2} + P_{H2O},$$

gas phase separation is possible. Stable, time-invariant levels of supersaturation were not thought to be physiologically realistic. Hills proposes that the gas phase would separate from the dissolved state on aqueous-hydrophobic interfaces that acted to lower the energy needed and to aid a reaction with an unfavorable entropy change. The effects of exercise on gas phase formation would not

appear in this type of analysis. DCS, however, would be increased because of coalescence of the separated gas into a larger free gas phase aided by muscle activity.

The concept of stress-assisted nucleation allows for the qualitative understanding of decompression gas phase formation, helps to explain the large difference between *in vivo* and *in vitro* gas bubble formation, and can also explain the predominance of lower extremity DCS. Such a mechanism has been postulated to be responsible for the genesis of a decompression gas phase in tissue. Theoretical treatments to describe this have been deficient, and we have recoursed to experimentation to obtain the requisite parameters. It was found that, depending on solubility, a supersaturation of several hundred atmospheres is required in pure water. This is considerably more than a change of 2 atmospheres in diving. Once a spherical bubble has formed, the conditions for stability are given by the Young-Laplace equation (cf. Harvey, 1951):

$$\Delta P = P_{gas} - P_{ambient} = 2\gamma/R,$$

where P_{gas} is the pressure of the gas within the bubble, γ is the surface tension of the fluid medium, and **R** is the radius of the bubble. Because of the effect of surface tension, the internal pressure of a gas bubble of **R** = 0.01 micron at 25°C is 143 atmospheres. Smaller, nascent bubbles would have considerably higher internal pressures. Unless the effective surface tension is considerably reduced at smaller radii, clearly some mechanism must deposit sufficient energy into a microvolume to bring the bubble through the formative process to a radius that can be stabilized by inwardly diffusing inert gas. Work **W** must be done on the system before a gas bubble of critical radius **R** can be formed. The work to form a cavity (bubble) in a fluid medium is given by (cf. Peyrou, 1967)

$$W = (16/3)\,\pi\gamma^3 / (P_{gas} - P_{ambient})^2.$$

Mechanical stresses have been proposed to assist in the performance of this work for the formation of decompression gas bubbles. Homogenous nucleation involves the rupture of water structure to create a cavity so that cavitation effected solely by supersaturated gas in water does not readily occur (Hemmingsen, 1975; 1977). In experiments where requisite supersaturations have been measured, the liquids serving as the solvent are always still (unstirred during decompression). Quiescence is not the normal case for living creatures.

Negative hydrostatic forces capable of rupturing the water structure (overcoming its tensile strength) in an environment free of nuclei can be created by mechanical forces. Nucleation that results from shock waves is the product of a rupture of the water structure induced by the tensile forces of compression and rarefaction. Shock waves might be produced in the lower appendages when the subject is walking. Tribonucleation (Hayward, 1967) can effect the formation of a gas phase when two surfaces are brought into contact with one another and are then separated. In a process described by Banks and Mill (1953; termed "tacky adhesion") and by Campbell (1968; termed "viscous adhesion") negative forces—which are tensions capable of overcoming the tensile strength of water—are generated when adjoining surfaces are separated. The forces experienced during withdrawal can be considerable (appendix).

Many authors have noted the poor quantitative correlation between the degree of supersaturation for gas phase formation in *in vitro* versus *in vivo* systems (Hemmingsen, 1989). Gas phase formation in pure liquids requires supersaturations of 100 to 200 atmospheres before a gas phase forms. The production of a gas bubble in a liquid is a process known as "cavitation" that first requires the creation of a void or cavity in the fluid. Water is unique in its high cohesive energy, which exists because of its hydrogen-bonded structure. To fracture pure water, the theoretical limit requires that the gas supersaturation be on the order of 200 to 4000

atmospheres [atm.] (Weathersby et al., 1982). Generation of a separated gas phase proceeds more easily when assisted by, for example, a physicochemical mechanism that reduces the energy required for gas phase formation or by mechanical forces.

These mechanical forces have been postulated to be responsible for the relative ease with which a gas phase forms in living tissue. The vast majority of evidence for muscle and joint activity as a provocative agent for stress-assisted gas phase formation derives from animal experimentation. Early work was directed towards the genesis of a gas phase in the aircrews of high-altitude bombers during World War II. Harvey (1951; Harvey et al., 1944) demonstrated the presence of tissue gas micronuclei in animals. Whitaker et al. (1944) and Harris et al. (1944) showed that rats and frogs that exercised at altitude displayed a greater number of vascular bubbles than those that rested. Exercise effected an increase in some tissue component (gas micronuclei or carbon dioxide), which decreased with time because exercise ***prior to*** decompression produced increased numbers of vascular bubbles in frogs. But the promotion of the formation of vascular bubbles decreased as the interval between exercise and depressurization lengthened. Vigorous activity of frogs also promoted the growth of a free gas phase following decompression from hyperbaric conditions.

Active and nonactive crabs responded in a similar manner to exercise and hypobaric decompression as indicated in studies by Evans and Walder (1969) and by Daniels et al. (1984). Genin (1948) noted the resistance of hibernating squirrels to altitude decompression bubble formation, and Vann et al. (1980) demonstrated that pressure spikes reduced the incidence of DCS in rats—an observation whose explanation is compatible with the hypothesis of tissue gas micronuclei. Work by Blinks et al. (1951) and Hemmingsen (1989) indicates that stable tissue gas micronuclei are of lesser importance and are overpowered by other mechanisms under physiological conditions. These physiological conditions are muscle and joint movements that are described above as "viscous adhesion." Experiments using crabs as subjects demonstrated a resistance to the formation of visible decompression gas bubbles (seen through the carapace) when the feet of the crabs were stabilized with epoxy adhesive. A similar decompression, when the crab's legs were no longer immobilized, produced numerous visible gas bubbles.

It is known that human volunteers display an increased tendency to DCS following exercise. A study by Ferris and Engel (1951) determined that the number of men who developed DCS in their lower limbs increased when they performed step (stair climbing) exercises at simulated altitude. The response was proportional to the degree of exercise, and there was also an indication that the subjects reached a plateau where further exercise did not produce an increase in the number of responders (or time of response).

It can be hypothesized that the considerably reduced activity of the lower extremities in microgravity results in a greatly reduced concentration of micronuclei and, therefore, of fewer tissue gas micronuclei during decompression.

C. *Sites of Origin of Doppler-detectable Gas Bubbles*

In the broadest anatomical sense, the sites of origin of all Doppler-detectable gas bubbles in *hypo*baric exposure in humans cannot entirely originate from connective tissues. We can make a rough calculation to determine this. Joint pain is generally associated with a precordial Spencer Grade IV. In trials where this volume was studied using sheep as subjects (Powell and Spencer, 1980), it was estimated at 2.5×10^{-2} kg/ml/min in sheep that were assayed by both air injection per catheter and following decompression. If similar physiologic principles hold, such precordial Grades would be associated with an infusion rate of gas bubbles into the pulmonary artery of 2 ml/min

for a 180 lb human subject. In that it is not unusual under hypobaric conditions for these grades to continue for 2 hours, that would be ~150 ml of inert gas (at standard temperature and pressure (STP)), a considerable amount since the human body contains only 600 to 1000 ml of dissolved nitrogen per atmosphere (which is the total amount excreted during oxygen breathing).

In accordance with Henry's law, the volume of gas that will dissolve is proportionate to the partial pressure of the gas, the solubility coefficient in a given solvent, and the volume of that solvent. While the solubility of nitrogen in living tissue is known with only varying degrees of precision, no known estimates would allow that much nitrogen to appear from the collagenous tendon and ligament tissue that is associated with the joint pain of DCS. We are left to conclude that the sites of origin of most Doppler-detectable bubbles lie in muscle and adipose tissue. Because muscle and tendon are kinetically and anatomically connected, it is reasonable to expect that some degree of relationship should exist between the Doppler-detectable phase and the joint pain of decompression.

This distribution of generated gas bubbles differ from that found in rats at necropsy by Powell (1972 b) for *hyper*baric exposure because, in a later case, gas bubbles were found predominantly in veins that drained abdominal muscle and adipose tissue sites. (Rats, however, have small limbs in comparison to their trunk and, after taking this into account, the distribution may not be unusual.) Microscopic examination revealed that this gas phase was exclusively intravascular in these cases and that it contributed the majority of Doppler-detectable gas bubbles (Powell and Weydig, 1974). In the case of hypobaric decompression, gas bubbles in the pulmonary artery are usually not detected until there is a movement of the extremities. This would indicate that the majority of Doppler-detectable gas bubbles are spawned in the arms and legs of subjects rather than in abdominal sites.

Since these showers of gas bubbles can persist for hours, it is difficult to imagine that they are emanating solely from tendons and ligaments, the supposed site of joint pain (Nims, 1951; Inman and Saunders, 1974). Since Henry's law links the volume of joint tissue (the solvent) and the solubility coefficient of inert gas, it follows that there is volumetrically insufficient connective tissue to produce the prolonged release of gas bubbles. If gas bubbles are spawned and released from connective tissue, they are diluted by gas bubbles from muscle tissue. Therefore, the nexus between Doppler-detectable gas bubbles and joint pain DCS is essentially a statistical, rather than a direct, one (Powell, 1974; Powell and Johanson, 1978; Nashimotoh and Gotoh, 1978).

Such a relationship holds for hypobaric decompression where the *probability* of DCS increases as the number of Doppler-detectable gas bubbles increases (fig. 1-2). This follows from the fact that, while the vast majority of circulating bubbles do not emanate from joint connective tissue, these circulating bubbles do emanate from anatomically related systems and often have similar cavitation tendencies.

It is known that only a statistical relationship, not a deterministic one, exists between Doppler-detectable vascular gas bubbles and joint pain DCS (Powell, Spencer, and van Ramm, 1982). From this we would deduce that the *in vivo* gas generators are mechanically coupled but are not identical (fig. 1-5). The origin of Doppler bubbles is intravascular and forms primarily from kinetically active (muscle) tissue (Powell and Spencer, 1980). Banks and Mill (1953) therefore postulated that viscous adhesion between the walls of the capillaries generates intravascular micronuclei. The movement of muscle tissue (or of any other movable tissue) will cause the momentary collapse of the capillary lumen with approximation of vessel walls (fig. 1-6). The later rapid expansionary movement of the walls will generate a momentary vaporous cavity. This gas micronucleus grows with the inward diffusion

of dissolved gas during decompression. The geometry of a collapsible tube of finite but varying length makes it difficult to calculate exactly the negative pressure generated.

A mechanism similar to this may have been indicated by Blinks, Twitty, and Whitaker (1951) who write,

> "Very gentle massage of isolated vein segments will also cause bubble formation under decompression. It is conceivable that muscular exercise may expose *fresh surfaces* in veins and arteries ...." (emphasis added).

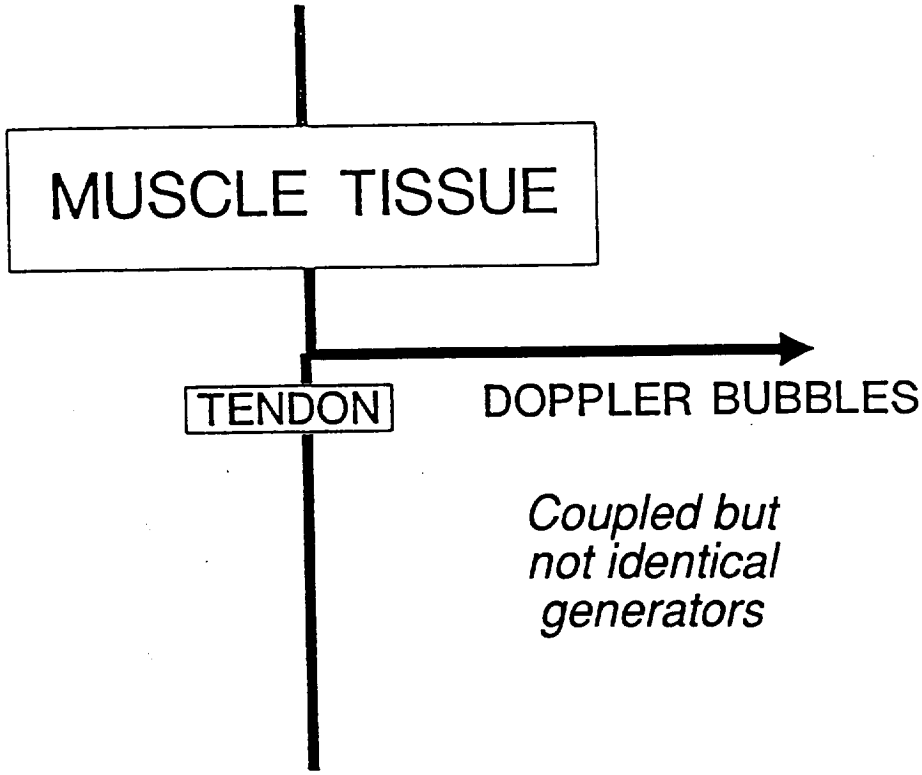


Figure 1-5. Generation of Doppler bubbles.

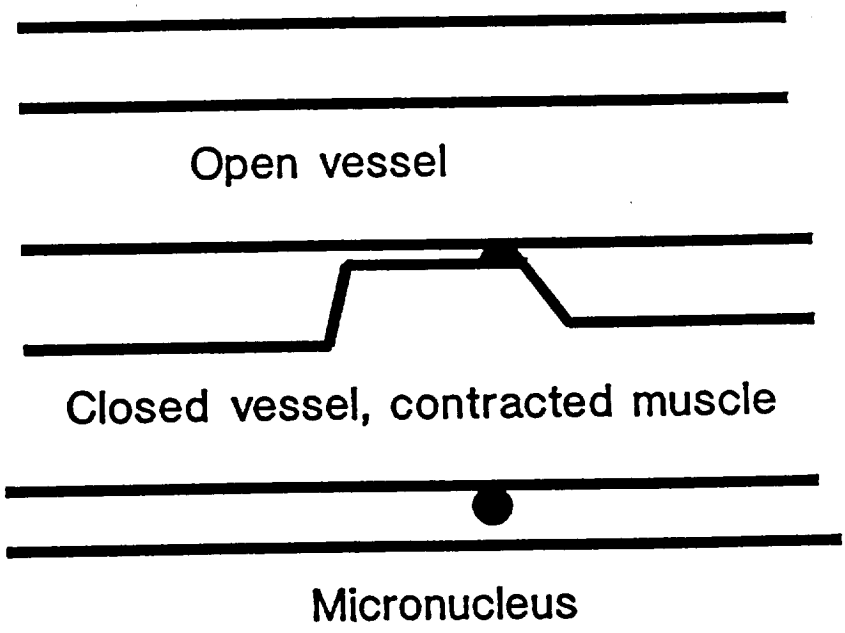


Figure 1-6. Formation by viscous adhesion.

Part II.

Decompression in Simulated Microgravity

Summary

1. Following decompression, bed rest reduces the amount of gas bubbles detected in test subjects by Doppler ultrasound flowmeters.

2. This reduction is usually associated with a smaller incidence of joint pain (although this is not proven for 3-day bed-rested individuals).

3. DCS was detected in subjects under both test conditions (bed rest and ambulatory).

4. Quantitative indications or recommendations for changes in current NASA procedures must be made cautiously because of the limited number of test subjects and the specific test conditions of Project ARGO.

I. Background

A. DCS Incidence During EVA

Joint pain DCS ("the bends") occurs as a result of the formation of a gas phase in connective tissue of diarthroses (Inman and Saunders, 1944; Nims, 1951; Hills, 1966). Blood-borne factors might also play a role (Philp, 1974). Some of these factors are of interest but, to date, have not been independently confirmed. From trends in the reported outcomes of decompression during EVA, astronauts appear to have a reduced risk of DCS following at least 3 days in microgravity compared to similar human experimental subjects who have lived and ambulated for at least 3 days at one g before decompression. Curiously, astronauts might even be expected to experience a greater degree of gas phase formation (and DCS) because of ionizing radiation and its effects on the promotion of phase transitions, as for example seen in gas-liquid bubble chambers (Peyrou, 1967).

Canonical, ground-based laboratory studies (Conkin et al., 1987) were conducted with human volunteers over a wide range of tissue pressures ratios. These studies were effected either by

(a) selection of the final pressure and a direct decompression to it, or

(b) washout of tissue inert gas by oxygen breathing followed by decompression to a final pressure.

Such studies have delineated both the incidence of DCS to be expected (fig. 2-1) and the degree of whole-body gas phase formation that occurs (Powell, 1991).

B. Reduced DCS Risk—Possible Explanations

To date, U.S. astronauts have performed 37 manned excursions for EVA that required significant decompression immediately preceding the activity. No reported incidences of even mild DCS have arisen. Several explanations have been posited.

1. Reduction by Nonphysiologic Possibilities

(a) An unawareness of any problem of joint soreness while intensely involved in EVA activities

PROBABILITY OF NO DCS

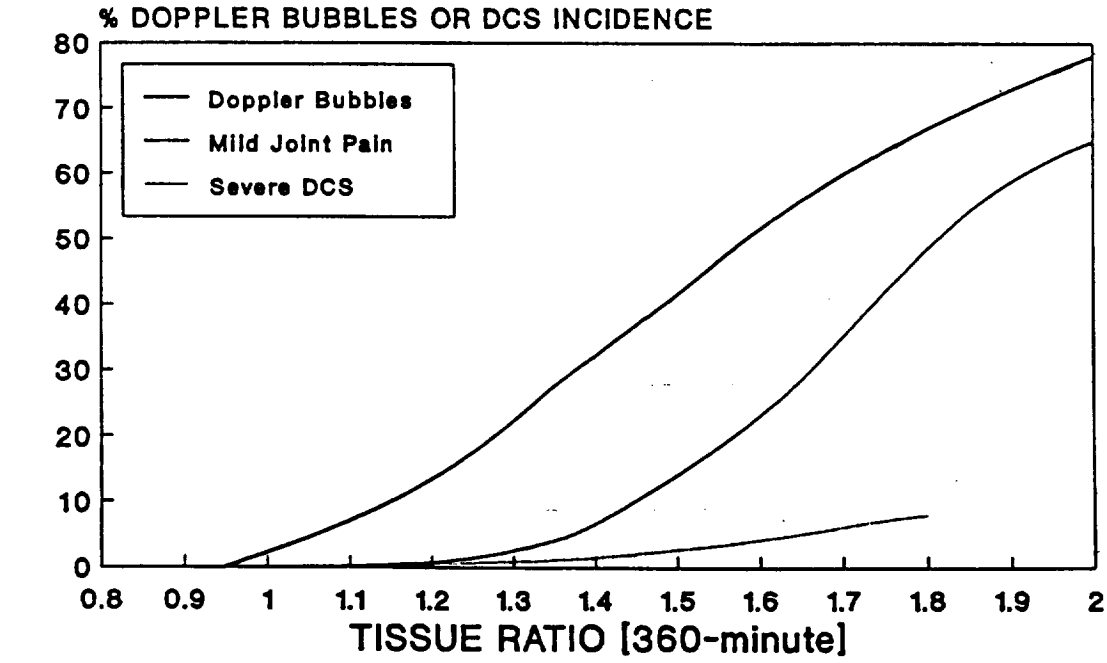
- 37 EVAs BY U.S. ASTRONAUTS & NO DCS

  SEVERE DCS p = 17%

  MILD DCS p = 10 exp [-5]

- 37 U.S. EVAs + 73 EVAs BY COSMONAUTS

  SEVERE DCS p = 2.8%



DCS AND MICROBUBBLES, N = 926
SEVERE DCS, N = 68

Figure 2-1. Decompression risk assessed at unit gravity.

(b) A statistically allowed cluster phenomenon of safe, DCS-free decompressions

2. **Reduction by Physiologic Possibilities**

(c) Repetitive decompressions by a set of individuals who are resistant to DCS

(d) Modification of ventilation-perfusion ratios in microgravity

(e) Cardiovascular changes (e.g., fluid shifts) that result in an increased rate of inert gas washout

(f) Use of mild analgesics

(g) A lack of tissue micronucleating agents and/or mechanism(s) for the growth of a tissue gas phase

3. **Discussion of Possibilities for Reduction of DCS**

(a) Unnoted Soreness

It is possible that mild, unnoted joint soreness could have occurred. Earth-based laboratory studies (at one g) indicate a 25% expected incidence of mild discomfort that could readily be discovered during an EVA. Volunteer subjects in ground studies are "coached" and urged to report any painful sensations in the joints. Such coaching would inflate the DCS incidence of mild problems. Most mild pains will resolve without residual symptoms upon repressurization in an air lock.

(b) Cluster Phenomenon

In Earth-based decompression studies, there was a 4.7% incidence of substantial joint pain that was sufficient to abort the altitude chamber trial and that required immediate recompression treatment. The possibility of "good luck" (cluster phenomenon) is statistically possible and cannot be eliminated at this time. The probability $f(x)$ of completing x successful—i.e., "bends free"—decompressions in n EVAs with a given failure rate, p, is given by the Bernoulli (binomial) distribution

$$f(x) = {}^{n}C_{x}\, p^{x} (1-p)^{n-x} \quad \text{for } x = 1,2,\ldots,n$$

From this it can be determined that currently an ~17% probability exists of not encountering a severe joint pain DCS problem during 37 EVAs. If we examine the experience of Russian cosmonauts (who have reported no severe DCS during 73 trials at an average TR = 1.8; incidence severe DCS = 5.6%), then $P_{success}$ = 1.5% for no severe DCS. The probability of successfully completing the entire series without *severe* joint pain DCS by **both** groups (N = 110) is even less ($P_{success}$ = 0.26%). From Earth-based results ($P_{success} < 10^{-6}$), *mild* DCS statistically should have been encountered, however.

(c) Repetitive Decompressions

Astronauts performing EVA procedures are not new individuals for each event. Calculations of expectation require that each event be totally and completely separate and unrelated. This would mean a requirement for essentially a "new" astronaut for each EVA. Chance may make these individuals resistant to decompression, a circumstance well known and encountered in diving.

(d) Gas Exchange

Portions of the body that require a long period of time to exchange inert gas—so-called long half-time "compartments," ($t_{1/2}$ = 360 minutes in hypobaric decompression—would not be measurably influenced by minor improvements in gas washout engendered by improvements in the ventilation/perfusion ratios.

(e) Perfusion Increases

Cardiovascular alterations in microgravity, such as fluid shifts, have been known to produce acute changes in tissue gas washout (Balldin et al., 1971; Balldin, 1973). Considerable research has been performed by physiologists interested in the effects of hyperbaric and environmental conditions on the performance of deep-sea divers. Much of the data collected in studies conducted to study the maximizing of gas washout conditions for deep-sea divers can be applied to microgravity conditions.

In the acute situation, immersion of the body and temperature influenced elimination. This increase was secondary to acute elevations of cardiac output and decreases in systemic vascular resistance (Arborelius et al., 1972). From measurements of mean arterial pressure, P_{sa}, mean right atrial pressure, P_{ra}, and cardiac output, Q, systemic vascular resistance, R_v, during seated immersion with the head above water (35°C) was calculated from

$$R_v = [P_{sa} - P_{ra}] / Q$$

Vascular resistance was found to decrease by 30% from air (dry) seated at 25°C to immersed seated while the subject breathes either air or oxygen. The mean increase in central blood volume in wet-seated to dry-seated conditions (air or oxygen breathing) was found to be 0.7 liters. Cardiac output increased in wet-seated over dry-seated subjects by 32% and stroke volume increased by 35%. Ambient temperature (25°, 28°, and 37°C) and body position (seated or supine) influence inert gas elimination (Balldin, 1973).

With readjustment over time in plasma volume, less of a gas washout increase is expected as cardiac output returns to normal. With water immersion, for example, most blood volume values return to the air-control conditions within 2 hours (Pendergast and Olszowka, 1989). In bed rest, as the analog for zero g, the plasma volume is normalized within several days (Rehbein et al., 1990). It is not experimentally known if this will be the actual occurrence in space.

An increase in *whole-body* gas washout does not necessarily imply an increased gas elimination in bends-producing tissue. Subjects who were put immediately into a -15° head-down tilt position at the initiation of decompression and oxygen breathing, and who stayed in this position for the remaining 3 to 6 hours, evinced neither a reduction in DCS nor in precordial Doppler-detectable gas bubbles (Iseyev et al., 1988). Even in acute head-down subjects, the incidence of DCS was not reduced when seated versus head-down supine individuals were compared (Vann, Gerth, and Leatherman, 1989). Fluid shifts are also produced in deep-sea divers as a consequence of their immersion. Such an immersed condition is generally associated with an *increased risk* of DCS (as long as the decompression phase does not occur while the subject is submerged).

(f) Use of Acetylsalicylic Acid (ASA)

EVA crewmembers are known to use ASA (aspirin) prior to depressurization. This mild analgesic would certainly aid in mitigating the discomfort of mild joint pain and would reduce the apparent incidence of DCS.

(g) Reduction of Stress-assisted Nucleation

It is known that the supersaturation limits for the production of a decompression gas phase *in vitro* in quiescent fluids exceeds by several orders of magnitude those limits for *in vivo* systems. Equilibrium thermodynamics has been no more adequate in describing phase changes in the formation of a gas bubble than it has been in elucidating the formation of ice crystals from supercooled water. The formation of gas bubbles has been attributed to the presence of microbubbles capable of serving as "seeds" upon which the tissue gas phase will later grow during decompression. The ad hoc postulation of the existence of these

quasi-stable, preformed microbubbles in living tissue forms the basis for at least two decompression systems; viz, the varying permeability model (Yount and Strauss, 1976) and the reduced gradient bubble model (Weinke, 1990). The origin(s) of microbubbles is unresolved, but *stresses* such as tensile force and tribonucleation are almost surely the major mechanisms.

A reduction in the effects of stress-assisted nucleation and/or the number of tissue gas micronuclei is a strong possibility. This would result from reduced activity (hypokinesia) in space of a subject's lower limbs and the lack of weight-bearing loads (adynamia) on a subject's legs. The ***abaroferric hypothesis*** is developed below. The term was coined from "a" (the negative) $\beta\alpha\rho o\sigma$ (weight, pressure) $\phi\varepsilon\rho\iota\xi$ (to carry, bear).

C. *Biophysical Mechanisms for the Reduction of DCS in Microgravity*

Exposure to weightlessness is known to impair the ability to tolerate postural changes, acceleration, exercise, and exposure to lower body negative pressure. Curiously, such exposure to zero g may be of some benefit in the area of susceptibility to altitude DCS. Currently three fundamentally different concepts exist that involve gas phase formation in supersaturated *in vivo* systems. These are

1. Metastable State

The concept of time-invariant stability, or the "metastable state," was first used by J. S. Haldane (Boycott, Damant, and Haldane, 1908) to calculate his decompression tables. For purposes of schedule calculation, Haldane proposed that a two-phase, gas-liquid system would not form if

$$P_{\text{dissolved inert}} < P_{\text{metastable limit}}$$

An inert gas partial pressure falling between the metastable limit (which was a fixed partial pressure) and the saturation pressure would not separate and produce DCS. More recent analyses of the rate of nucleation J yield mathematical relationships of the type developed by Volmer-Becker-Döring; namely,

$$J = BP_o \exp\{-[16\pi\gamma^3 v^2] / ([3kT]^3 [\ln(P/P_o)])\}$$

where v is the molecular volume, P/P_o is the supersaturation, and the other terms have conventional meanings in physical chemistry. These produce results *similar to* the classical "metastable limit" of W. Ostwald and not the results seen experimentally in decompression physiology. Therefore, this approach is not believed to be correct, and the "metastable limit" is not affected by mechanical motion (muscle activity). This concept of the metastable state would <u>*not*</u> *recognize a difference in gas phase formation between unit and microgravity situations.*

The metastable-state concept has been *largely abandoned* as an explanation for the appearance of DCS. The formalism of the idea is successfully employed, however, almost universally in the algorithm that generates decompression tables for both altitude and deep-sea diving. This algorithm is easy to conceptualize, and its calculations are easy and straightforward to perform.

2. Random Nucleation

The formation of a gas phase at a hydrophobic interface was a concept advanced by B. A. Hills (1966) in his "thermodynamic model." In its entirety, the model included (a) phase equilibration of dissolved and separated gas, (b) radial perfusion-diffusion of capillary gases across cell membranes, (c) Bessel-exponential functions to describe gas fluxes, and (d) limit points for the elicitation of pain by separated gas volumes. Hills proposed that whenever

$$P_{\text{ambient}} < P_{\text{inert}} + P_{CO2} + P_{O2} + P_{H2O}$$

gas phase separation is possible. Stable, time-invariant levels of supersaturation are not thought realistic. Hills proposed that the gas phase would separate from the dissolved state on aqueous-hydrophobic interfaces. These interfaces would function to lower the energy needed and to aid a reaction with an unfavorable entropy change. The effects of continued exercise under unit gravity stress on tissue gas phase formation would not appear in this type of analysis.

The production of DCS would follow from a coalescence of the separated gas into larger gas "bubbles." This coalescence would be aided by muscle activity. As developed here, the concept would not predict a difference between unit and microgravity decompressions in terms of Doppler-detectable gas bubbles, but there might be a difference in the production of joint pain with exercise.

3. Stress-assisted Nucleation

This mechanism allows for the qualitative understanding of decompression gas phase formation, and it helps to explain the large difference between *in vivo* and *in vitro* gas bubble formation. Gas phase formation in pure liquids requires supersaturations of 100 to 200 atmospheres before a gas phase forms (appendix). The model states that *in vivo* viscous (or "tacky") adhesion supplies the energy required to overcome the surface tension of a microbubble. Powell and Spencer (1980) noted that gas bubbles were seldom detected by Doppler ultrasound from organs that did not move (e.g., kidney and brain) but were in profuse evidence from muscle tissue.

The need for considerably reduced activity of the lower extremities in microgravity results in a greatly reduced concentration of micronuclei and, therefore, in fewer tissue gas micronuclei during decompression. The micronuclei thus produced probably have a lifetime of several hours. The most telling evidence of their presence lies in the growth of visible gas bubbles by means of the phenomenon of **isobaric countertransport** (Lambertsen and Idacula, 1975).

II. Design of Project ARGO and Experimental Methods

A. General Plan

The hypokinesia study consisted of 3 days of reduced activity of the postural muscles of the subjects followed by hypobaric decompression on the fourth day. The bed-rest group "crossed over" and remained ambulatory for at least 2 weeks. Prior to entering the experimental series, each subject volunteer was required to pass the United States Air Force (USAF) Class III flight physical. Test subjects also participated in a familiarization trial to determine if they had any difficulty with the exercise procedures. This allowed the volunteer subjects to be able to judge their responses to the exercises with regard to joint discomfort, fatigue, myalgia, etc.

B. Subjects

The subjects were healthy adult men and women, 25 to 55 years old who were volunteers recruited from the Houston community. They were selected to match the astronaut population as much as possible in age, sex, height, weight, body surface area, percent body fat, and physical fitness level. Subjects were screened for the presence of patencies in the interatrial septum by means of B-mode ultrasound. Individuals with a patency were not excluded. Some individuals were lost because of relocation out of the area; they did not complete the paired study but were listed for completeness in table 1-III.

Subject participation in the project was voluntary, and the subjects could withdraw from the experiment at any time. Subjects were asked to sign the Human Research Informed Consent form after they had read the information package and received a subject briefing.

C. Bed-rest Experimental Protocol

The subjects were randomly assigned either to Group A_1 [bed rest] or to Group C_2 [ambulatory controls]. Half of all test subjects began as "bed rested" with the remainder acting as "controls." A minimum of 2 weeks intervened between the repeat appearance of a subject in one group or the other. The groups are as follows:

1. Group A. Bed rest: Hypokinetic and adynamic individuals who experienced cephalic fluid shifts.

2. Group C. Ambulatory controls: Individuals from group A who crossed over. Normokinetic and normodynamic individuals who underwent normal activities for daily living.

Bed-rested subjects remained at the hospital for this portion of the protocol. Bed rest was at -6° head down. All bodily functions (eating, drinking, defecation, urination, baths, etc.) were provided without leaving the bed; subjects could sit up for 5 to 10 minutes to perform these.

Subjects were instructed to reduce, but not eliminate, movement of their lower extremities, particularly any attempts to elevate their legs. These bed-rested test subjects could move their arms, however. Television, videos, books, and magazines were used to reduce boredom. No form of muscular exercise was permitted.

D. Hypobaric Exposure

Four days later, one bed-rested subject at a time was exposed to a reduced pressure of 6.5 psi ($TR_{t1/2} = 360 = 1.78$) for 3 hours in a hypobaric chamber by direct decompression (no prebreathe period). These bed-rested subjects did not walk but were transported into the chamber via a stretcher. An ambulatory subject also participated in each hypobaric chamber run.

All subjects breathed 100% oxygen while performing simulated EVA exercises (upper body) for 3 hours. The test frame holding the exercises was designed such that the exercises could be done while the bed-rested individuals were recumbent.

Test subjects were questioned at 1-hour intervals regarding the appearance of any joint pain. However, they could volunteer information at any time. Symptoms of Type I DCS were graded according to the following customary NASA/JSC scale:

- Grade 0: No symptoms.

- Grade I: Awareness of joint, but frank pain not present.

- Grade II: Mild discomfort that does not interfere with the performance of tasks.

- Grade III: Frank pain that interferes with the performance of tasks.

Upper body exercise of the type currently being employed in NASA/JSC hypobaric studies (e.g., crank turning, torque wrenches) was performed in the chamber by both test groups. Metabolic levels, which were measured in laboratory trials at a separate time, were in the range of 175 [Kcal./hr] for the ambulatory individuals and 150 [Kcal./hr] for bed-rested individuals. This was in addition to the normal maneuvers used to release gas bubbles spawned in the microcirculatory system during Doppler monitoring.

The experimental endpoints for the tests were

1. Completion of the 3-hour test with no symptoms up to and including Type I (joint pain), Grade I.

2. Type I (joint pain) with Grade III pain.

3. Type II (neurologic or cardiopulmonary) DCS.

E. Precordial Doppler Monitoring

1. Monitoring for tissue gas phase formation was performed with the standard precordial Doppler ultrasound techniques (Powell et al., 1982) employed at NASA/JSC in previous hypobaric trials (Conkin et al., 1987). The detection instrument was a MedaSonics *Transpect* operated with a 2 MHz transducer. Pulsed and continuous wave methods were tried with no clear advantage found for either, but variations would exist among test subjects such that one mode might be considered optimal for an individual. The resultant Doppler signal was analyzed both aurally and with the fast Fourier transform (FFT) output from the *Transpect* (fig. 2-2). In this diagram, an "*" indicates a bubble and a "V" indicates a heart valve (artifact).

2. Data collected from the Doppler monitoring were analyzed pair-wise by the method of integration of Doppler signal intensity versus time (time/intensity Doppler "gas volume;" Powell, 1991). Additionally, we noted the presence or absence of DCS in the subjects.

III. Results

Goals and results are summarized in figure 2 -3.

A. Decompression Sickness

1. Bed Rested

(a) There was one reported case of mild joint pain DCS in a bed-rested subject. This resolved upon repressurization to site level at the conclusion of the 3 hours.

(b) There was one case of abdominal rash in a subject (WF) who also exhibited orthostatic instability. This individual did not exhibit individual discrete bubble signals with the Doppler system but, rather, had a general intensification ("brightening") of the precordial Doppler FFT signal indicative of tens of thousands of microbubbles (Chimowitz et al., 1991). WF was positive for a "resting" PFO (that is, an augmentation maneuver—Valsalva and release—was not required for the transfer of bubbles) by saline echo contrast. The connections are apparent but are not conclusive at present.

2. Ambulatory

Among the ambulatory subjects, there was one case of Type II DCS involving a paresthesia in the left leg. This resolved upon repressurization to site level. Gas bubbles in the left ventricle were detected upon saline contrast echocardiography and simultaneously in the middle cerebral artery (MCA). In this subject, the passage of gas bubbles across the interatrial septum occurred "resting;" that is, during spontaneous breathing while supine. An augmentation maneuver (Valsalva and release) was not required for the transfer of bubbles.

It would not be expected that erect or recumbent positions would account for differences in the incidence of DCS, even if postural changes were acute and central fluid shifts occurred (Vann et al., 1989).

B. Doppler Detection of Circulating Microbubbles

A summary of Doppler test results is given in table 2-I. Gas bubbles were often heard in both ambulatory and bed-rested subjects; but, when this occurred, the grade and/or duration were less for bed-rested than for ambulatory subjects (fig. 2-4).

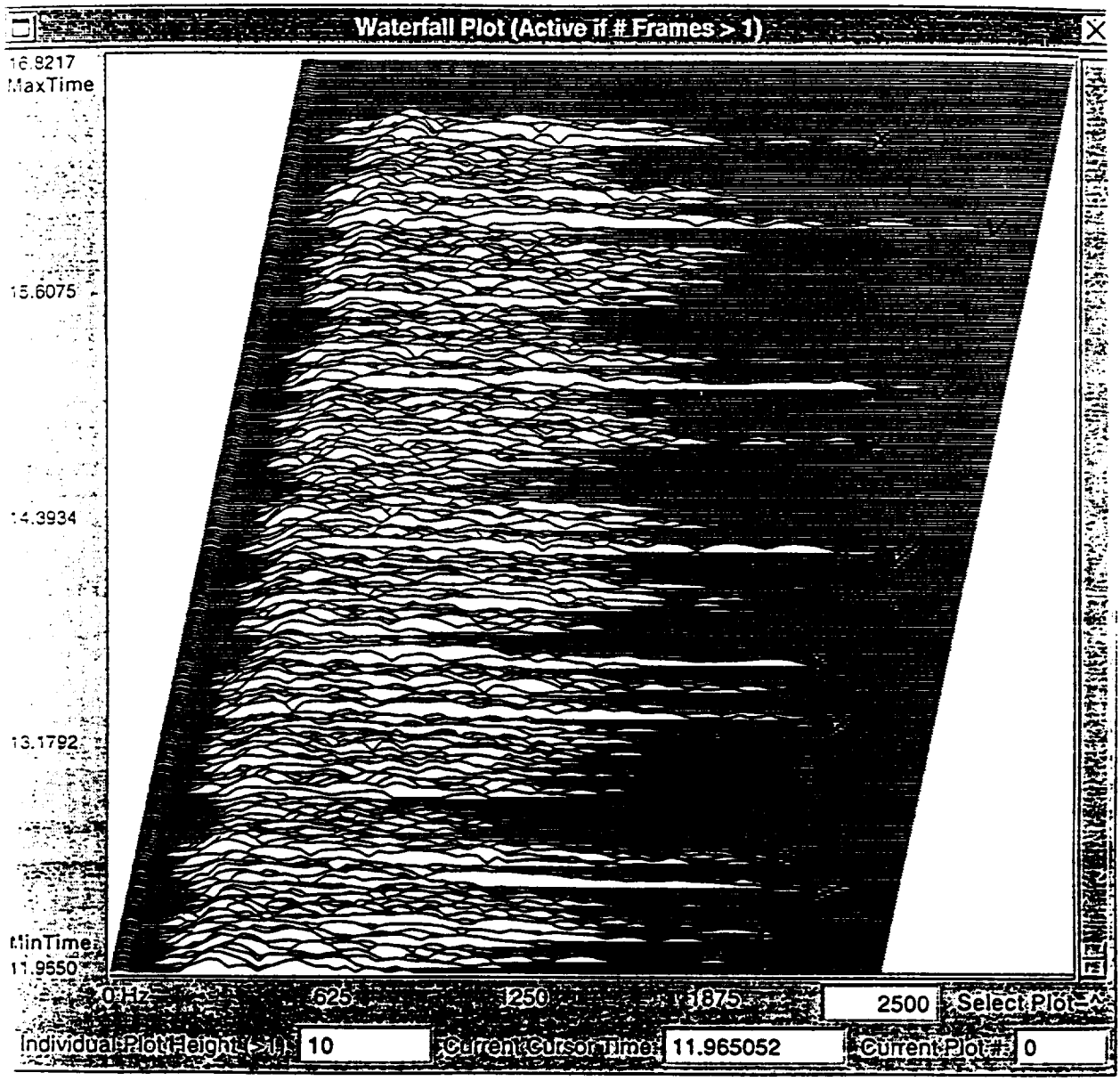


Figure 2-2. Waterfall plot (active if no. frames >1).

PROJECT ARGO

• FROM AN ANALYSIS OF THE AMOUNT OF DOPPLER BUBBLES, IT IS POSSIBLE TO DERIVE AN "EFFECTIVE" OR APPARENT TR FOR BED-RESTED SUBJECTS.

• THEY RESPOND, WITH RESPECT TO THE NUMBER OF BUBBLES PRODUCED, AS IF DECOMPRESSED TO A *TR OF* 1.27.

• TO ACHIEVE THIS WITH AMBULATORY TEST SUBJECTS *WOULD REQUIRE AN ADDITIONAL 175 MINUTES OF OXYGEN PREBREATHING.*

PROBABILITIES OF COMPLETING A SERIES OF MISSIONS WITHOUT DCS

• WITH THIS NEW, "EFFECTIVE" TR, IT IS POSSIBLE TO RECALCULATE THE EXPECTED INCIDENCE OF DCS.*

• DCS CALCULATED FROM TR DATA OF CONKIN et al. (1987):

Mild DCS	=	2.5%
Severe DCS	=	1%

• PROBABILITY OF NO *MILD* DCS IN 39 EVAs	=	37%
IN 110 EVAs	=	5%+
NO *SEVERE* DCS IN 39 EVAs	=	8%
IN 110 EVAs	=	30%

+ Includes the Soviet experience.

PROJECT ARGO

WHAT IT DOES NOT DO:

• IT DOES NOT HAVE SUFFICIENT STATISTICAL POWER TO STATE THE *CONFIDENCE* OF THE DCS INCIDENCE.

• IT DOES NOT DEMONSTRATE THAT GAS PHASE FORMATION IS REDUCED *IN SPACE DURING EVA.* [This requires the in-suit Doppler system.]

• *IT DOES NOT INDICATE THE SHAPE* OF THE CURVE FOR INCIDENCE versus TR OR THE *LINEAR SHIFT* ALONG THE TR AXIS.

NEUROLOGICAL PROBLEMS

• *SEVERAL* SUBJECTS PRODUCED A RELATIVELY LARGE NUMBER OF GAS BUBBLES THAT WERE DETECTABLE IN THE VENOUS RETURN.

• THESE ARE POTENTIAL EMBOLIZING AGENTS SHOULD THEY PASS INTO THE ARTERIAL CIRCULATION.

• THE CONDITIONS FOR RIGHT-TO-LEFT SHUNTING ARE NOT WELL CHARACTERIZED FOR HYPOBARIC DECOMPRESSION.

• SUBJECT AWARENESS AND/OR TREATMENT CAPABILITIES ARE NOT OPTIMAL IN SPACE AT PRESENT.

Figure 2-3. Goals and results.

Table 2-I. Summary of Doppler Test Results

NAME	MAXIMUM DOPPLER GRADE	
	Ambulatory	Bed rested
1. GH	0 (1)	0 (7)
2. KW	III (6)	0 (2)
3. DM	III (2)	0 (4)
4. LD	IV (15)	IV (3)
5. BH	0 (3)	0 (10)
6. SB	III (4)	II (5)
7. DB	0 (5)	0 (6)
8. WB	IV (7)	Withdrawn from study
9. SB	IV (11)	0 (8)
10. KH	0 (8)	Lost to follow-up
11. CK	0 (10)	0 (9)
12. DS	0 (9)	Lost to follow-up
13. DF	III (13)	II (12)
14. PL	IV (12)	0 (13)
15. JS	Lost	0 (14)
16. KG	0 (14)	0 (11)
17. TJ	0 (19)	0 (15)
18. KC	0 (19)	0 (16)
19. TO	0 (16)	Lost to follow-up
20. WH	III (21)	III (17)
21. WF	Withdrawn	"0"* (18)
22. CA	0 (18)	0 (23)
23. MS	IV (20)	0 (22)
24. KA	IV (22)	0 (20)
25. DK	IV (24)	II (21)
26. JA	0 (23)	0 (24)
SUMMARY:	**Precordial Grades**	
	0 = 12	0 = 17
	I = 0	I = 0
	II = 0	II = 3
	III = 5	III = 1
	IV = 7	IV = 1
Bubbles found:	12/24 individ.	5/22 individ.

*Microbubbles are believed to be present; incompatible with the Spencer grading system.

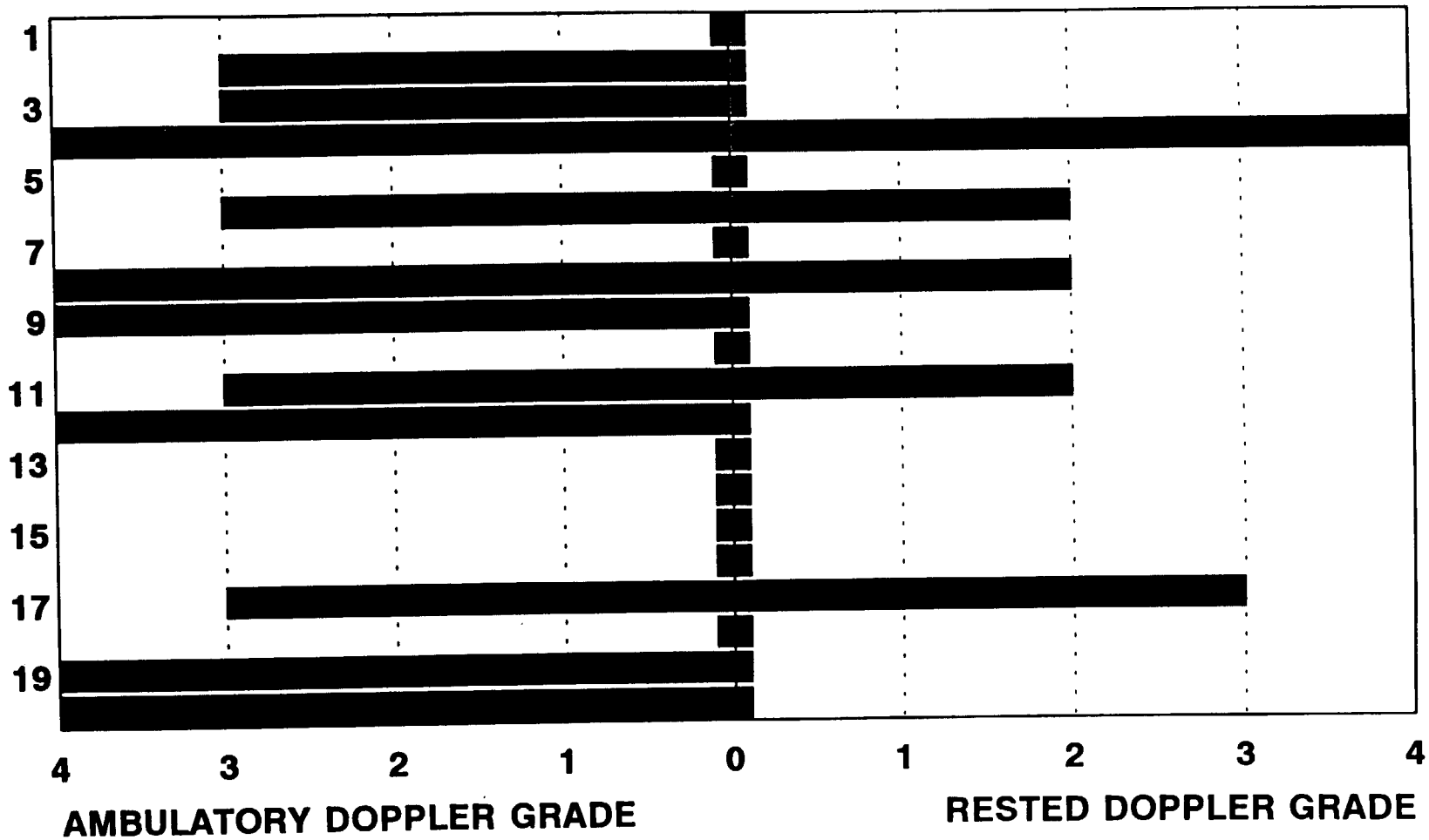


Figure 2-4. Spencer precordial Doppler Grade for ambulatory and bed rest.

C. *Time-intensity Analysis of Doppler Data*

We analyzed the Doppler ultrasound bubble detection data with the *time-intensity* [integration] method (Powell, 1991). The results are indicated in figure 2-5 where we note that there was a considerable reduction in the number of detected circulating microbubbles in the bed-rested subjects compared to the ambulatory subjects. In *all 20* paired exposures, individuals under simulated microgravity condition (bed rest) produced a smaller Doppler-detectable gas phase (in some cases, a Grade 0) than these same individuals when they where active and ambulatory.

To gain a knowledge of the degree of change from the expected amount of circulating microbubbles, the results of this test have been plotted along with other NASA/JSC data (taken from Conkin et al., 1987) on a log-log plot (fig. 2-5). The Doppler "gas volume" for the group of individuals decompressed to any given altitude is compared to a calculated TR for "compartments" of differing gas elimination halftimes. The TR is calculated at the time of reaching altitude and is based on the sum of the TRs for the 360- and 520-minute halftime compartments. This analysis assumes that joint pain DCS is a continuous function without a lower bounded P/P_0.

Reporting of NASA data is such that Doppler-detectable bubble incidence can be divided into upper and lower extremities (fig. 2-6) and into the lines through the points described by power functions of the type

$$f(x) = A\,x^B$$

In the case of individuals ambulating in unit gravity, the Doppler "gas volume" from all four extremities together is given by

$$^{All}GV_{Doppler} = (8.84 \times 10^{-3})\,[TR_{360+520}]^{3.97}$$

and r = 0.81. It is possible to determine the "gas volume" of the extremities of subjects all NASA studies. The power function for the upper extremities alone is

$$^{Arms}GV_{Doppler} = (6.63 \times 10^{-5})\,[TR_{360+520}]^{6.97}$$

with r = 0.76, and, for the lower extremities,

$$^{Legs}GV_{Doppler} = (2.90 \times 10^{-3})\,[TR_{360+520}]^{4.55}$$

with r = 0.81.

The Doppler "gas volumes" calculated for the upper and lower extremities of the group of subjects in simulated microgravity are 0.27 and 0.45, respectively, and the combined value is 0.303. As would be expected, there is a greater reduction in the tendency towards gas phase formation in the lower extremities than in the upper extremities of the individuals tested.

D. *Doppler Ultrasound Analysis*

Since much of the NASA and USAF data has been analyzed on the basis of Doppler bubbles—that is, on bubbles either being present or absent from a test subject—a graph with a similar type of analysis is included here (fig. 2-7). This graph indicates that the "apparent" TR is approximately 1.3 in bed-rested individuals.

IV. Discussion

A. *Statistical Difference*

As evidenced by this study, there was a difference between the tendency to form a Doppler-detectable decompression gas phase in bed-rested subjects compared to ambulatory individuals. Using a *chi*-square test after we grouped the Doppler results into Grades 0 - II and III - IV, we find the differences between ambulatory and bed-rested subjects is significant, at the p = 0.05 level.

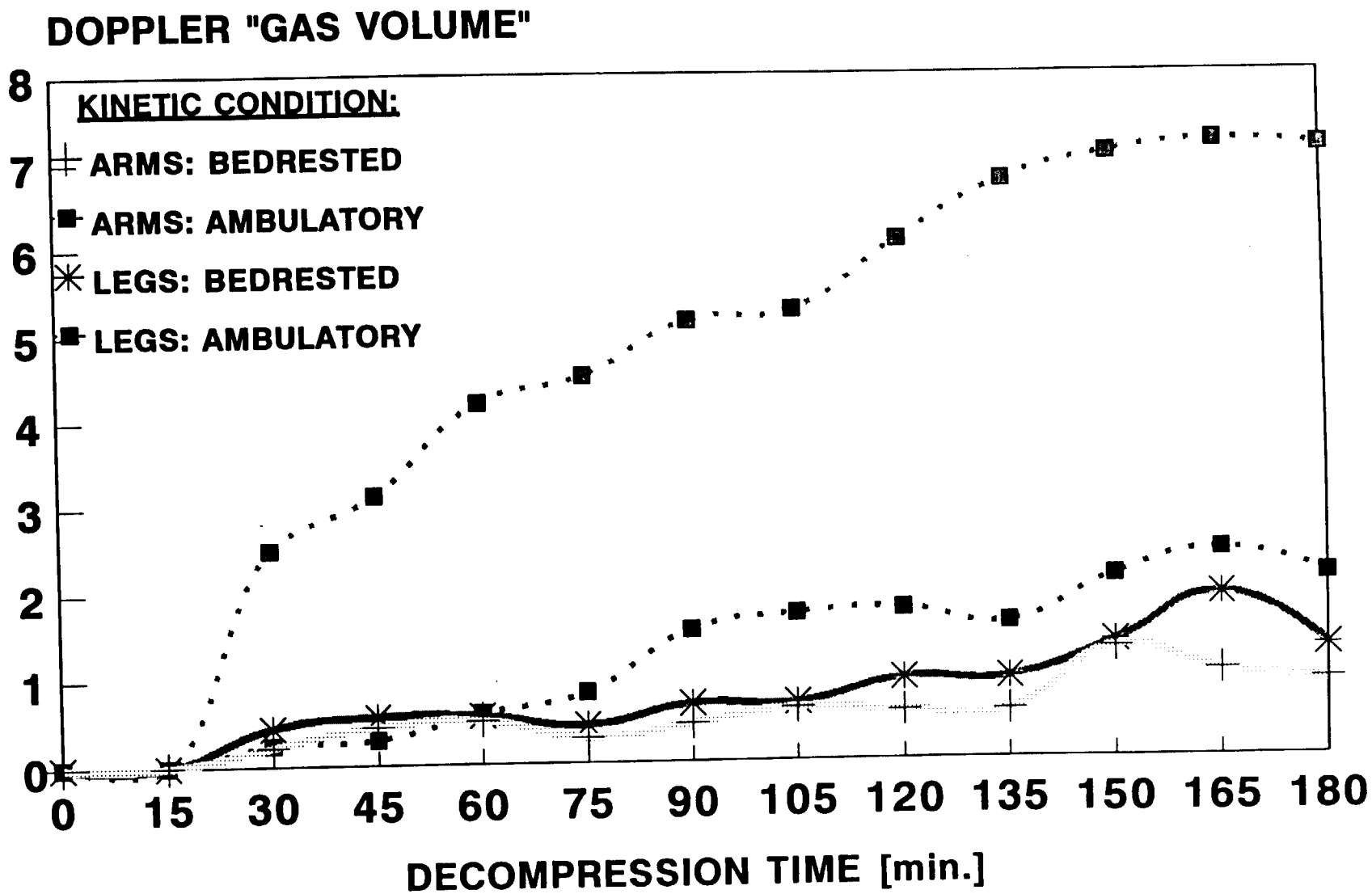


Figure 2-5. Decompression stress in ambulatory versus hypokinetic individuals.

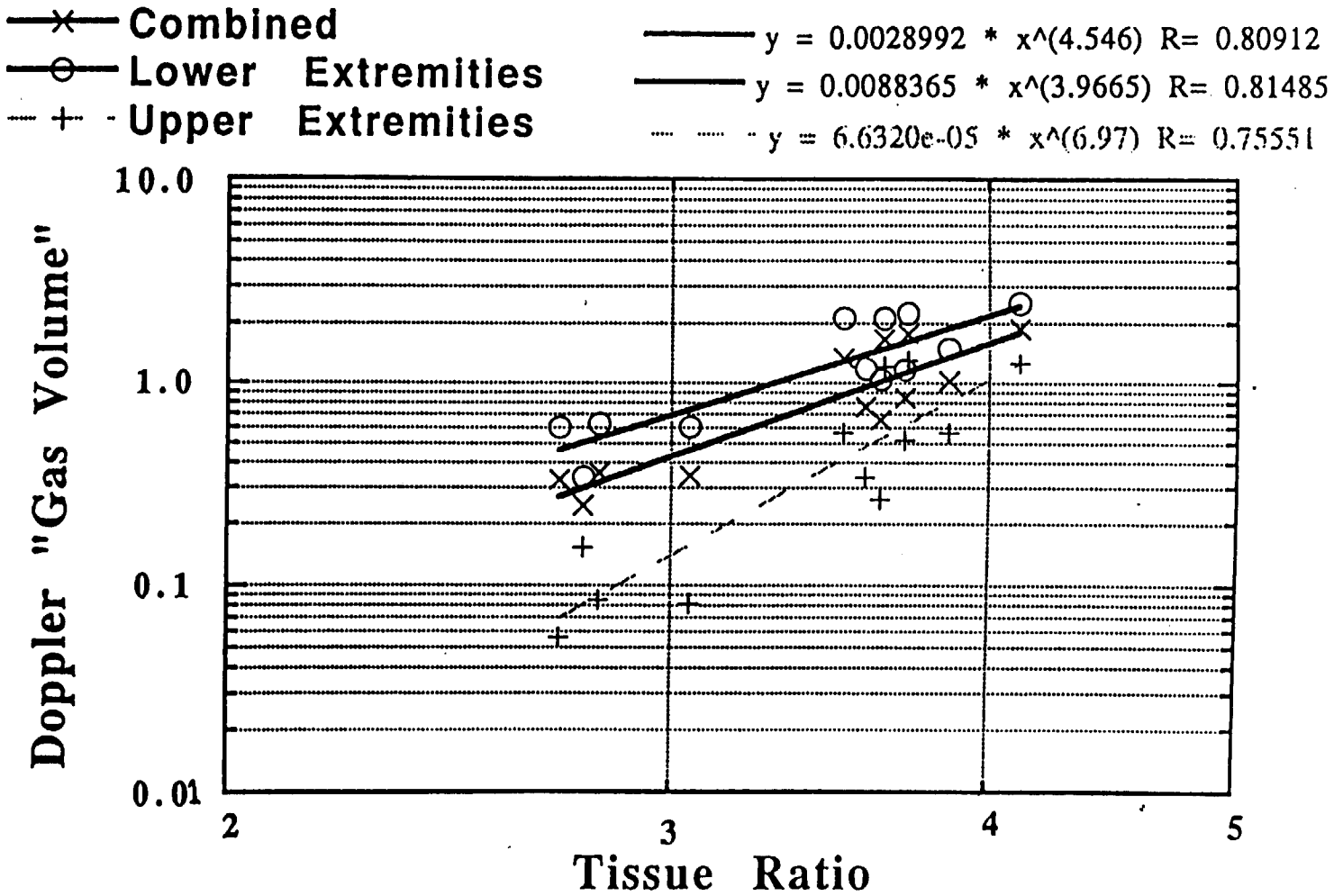
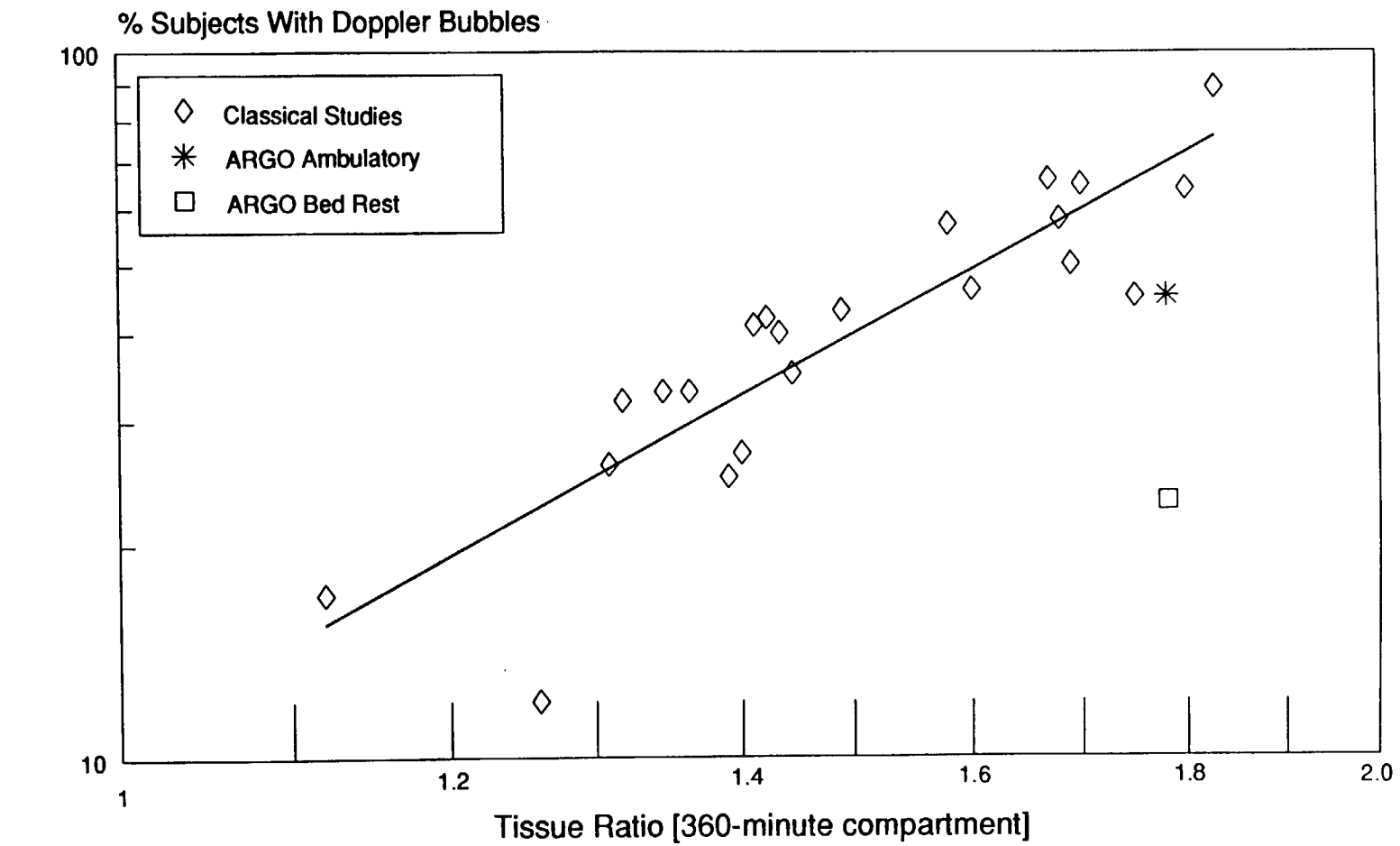


Figure 2-6. Doppler-detectable bubble incidence divided into upper and lower extremities.



Combined NASA and USAF data.

Figure 2-7. Doppler bubbles versus decompression TR.

While this does not prove the existence of either short-lived or stable, long-lived tissue micronuclei, this difference in bubble formation is consistent with their reality. Their loss would be predicted by a hypothesis connecting a reduction in their tissue concentration to a reduction of musculoskeletal activity. To our knowledge, this is the first demonstration of the apparent ability to modify the course of a decompression and to manipulate tissue micronuclei concentration by a means other than direct hydrostatic compression (or simple oxygen breathing).

B. *Hypothesis for the Mechanism of Action of the Abaroferic Hypothesis: The Stoichiometric or Modified Critical Volume Explanation*

During decompression, gas must remain dissolved and must not be evolved as free gas. Gas exchange by blood transport, and without diffusion barriers, is driven by the instantaneous local gas partial pressure gradient between the tissue p and the arterial blood p_a of the capillary. This is modeled for time t by simple classes of exponential response function of the form (appendix)

$$dp/dt = -\phi (p - p_a)$$

This has a solution that tracks both dissolved gas uptake and elimination and is of the form

$$p - p_a = (p_i - p_a) \exp (- \lambda t)$$

where

$$\phi = 0.693/\tau$$

or

$$\phi = \ln 2/\tau$$

τ is termed the *tissue halftime,* and, depending upon the model's range of pressures and times, it customarily takes values from 5 to 700 minutes.

These equations require that all dissolved gas remains in solution in both the cells and the bloodstream. No doubt, there is some shunting of dissolved gas into the micronuclei reservoirs or "sinks." Exactly how much shunting occurs is a requirement of table design. We are not currently at the point of preparing a universal (time-dependent) model. Gas phase formation will occur if the sum of the partial pressures p_i exceeds the ambient pressure P, or if

$$\Delta p = \Sigma(p_i) - P$$

If we consider cases where kinetic activity exists in the fluid, negative pressures p_{neg} can exist and increase the size of ΔP so that

$$\Delta P = \Sigma(p_i) + p_{neg} - P$$

We are primarily concerned with the growth of micronuclei during depressurization since gas uptake is at a saturation level; that is, all individuals have been exposed to sea-level gas pressure for at least several days. Weinke (1989) discusses the dynamics of a mixed dissolved/free gas, two-phase system as part of an algorithm he calls the "reduced gradient bubble model." In this, the dynamics of the free gas are characterized by η_{reg}, η_{rep}, and η_{exc}, which represent multipliers for the time, respectively, for *de novo* regeneration of micronuclei, for the lifetime for nuclei from a previous decompression to influence the next decompression, and as a term to describe deep-to-shallow dive progressions.

η_{reg}, τ = 14 days
η_{rep}, τ = 40 minutes, and
η_{exc}, varies with the dive

where τ is the characteristic halftime.

We might consider the change in equilibrium size of tissue micronuclei with time. These tissue micronuclei would attain a new radius r_{0g} that is controlled by muscular activity or tissue constituents, although it is not clear why constituents would change in zero g. The change in radius of a nucleus from its unit gravity value r_{1g} to the zero g value of r_{0g} with the passage of time t would then be given by

$$r_{0g} = r_{1g} + (r_{0g} - r_{1g})(1 - \exp[-\lambda_r t])$$

where λ_r is the inverse of the time constant for the change in diameter of all nuclei. With a different formulation, we might consider essentially the complete elimination of one species (viz, r_{1g}) and the formation of a new species (viz, r_{0g}) according to

$$r_n = r_{1g}(e^{-[k't]}) + r_{0g}(1 - e^{[-k''t]})$$

More probably, the problem might be represented by a change in the concentration of micronuclei n, possibly of the same size, r_{1g} when in zero g. The distribution of these sizes, numbers, and concentrations is not currently known. In the varying permeability model of Yount, different radii influence different exposures (pressures). The distribution is estimated to follow

$$n = N_{1g} e^{[-\xi r]}$$

where ξ is a constant. In zero g, N_{0g} replaces N_{1g}. Further, we postulate that

$$N_{0g} < N_{1g}$$

We will now discuss the volume of free gas evolved in tissues (and in an *in vitro* model) during a step decrease in pressure.

1. Decompression of a Saturated Liquid

To view the decompression process, let us consider a simple *in vitro* model, a case where a volume of a liquid that is saturated with an inert gas (solubility = β) is enclosed in a container with a gas-tight piston as a lid. The liquid is saturated at pressure P_i, and an external pressure is applied to the piston to retain the inert gas in solution. If the external pressure were suddenly reduced to pressure P_f, a free gas phase would form in the vessel and the piston would eventually rise to produce a volume V in accordance with Henry's law. It was originally shown by Hills (1966) that a mass balance for the process could be given by the following equation, which accounts for equal moles of gas on both sides of the equation:

$$\beta P_i = \beta P_f + V P_f. \qquad [1A]$$

Dividing by β gives,

$$P_i = P_f + (V/\beta) P_f \qquad [2A]$$

Rearranging terms gives

$$(P_i/P_f) = (1/\beta) V + 1 \qquad [3A]$$

which would allow us to compute the solubility β of the gas by measuring the total released volume at each P_i/P_f. A plot ($y = mx + b$) would give the slope $m = (1/\beta)$, and the intercept $b = 1$ if

(a) No inert gas-saturated liquid was lost from the apparatus, and

(b) Supersaturation did not occur.

This is graphically depicted in figure 2-8.

2. Gas Volume with Supersaturation of the Liquid

If the volume of liquid in our *in vitro* model should remain supersaturated following decompression, a lesser volume **V** of free gas would be released. Complete supersaturation would mean that no free gas was released. (A free gas phase is released into tissue in the *in vivo* case to cause joint pain. Increased supersaturation would be promoted by a lower density of micronuclei that can grow during supersaturation.) The equilibrium would be given by the following equation, where σ is the degree of supersaturation:

$$P_i \beta (1 - \sigma) = (1 - \sigma) P_f \beta + V P_f \qquad [4A]$$

Rearranging the terms as before in Equation [3-A] gives,

$$P_i/P_f = [1 /(1 - \sigma)] [V/\beta] + 1 \qquad [5A]$$

If we were to determine gas solubility from measuring the released volume **V** in the *in vitro* model, the computed value would be too small by $1/(1 - \sigma)$. If we wait a sufficiently long time, the supersaturation will be reduced. Indeed, at time = ∞, $\sigma = 0$, equation [5-A] will be reduced to equation [3-A]. This is shown graphically in figure 2-9.

Physiologically, a large ***allowable supersaturation*** translates into large allowable pressure changes; that is $P_i/P_f >> 1$. For the hypobaric case, this would mean TR values greater than 1.8 would be allowable or "safe." If gas bubbles cannot form *de novo* but must grow from micronuclei, the number N_{0g} of these is critical and, naturally, $\sigma = f(N_{0g})$.

3. Decompressions with Loss of Saturated Fluid

If some fraction λ of the saturated fluid is withdrawn in the *in vitro* model, the volume of free gas produced will be less. The mass balance equation for this is

$$P_i \beta(1 - \lambda) = (1 - \lambda)\beta P_f + V P_f \qquad [6A]$$

The loss would be related to the fractional volume λ of liquid removed. With no supersaturation, but with loss λ,

$$P_i/P_f = \frac{[V/\beta]}{(1 - \lambda)} + 1 \qquad [7A]$$

The difference between equation [4A] and equation [7A] is that the volume of gas collected in the latter case would be *less* and the collection would *not be time dependent*. That is, waiting for a period of time would *not* increase the collected gas volume because the system would already be at equilibrium. In the *in vivo* case, the loss-of-fluid situation is equivalent to the removal of dissolved inert gas by the bloodstream. Once lost, this dissolved inert gas could naturally never appear in the tissues as free gas and effect the growth of bubbles.

A diagram depicting a given degree of supersaturation, but with varying amounts of loss of gas-saturated fluid, is shown in figure 2-10.

4. *In Vivo* Situations

The above situations were mostly concerned with the *in vitro* model of gas recovery from a decompressed fluid. For *in vivo* decompression from altitude, the endpoint will usually be determined by the presence or absence of DCS. For the case where pain only DCS ("the bends") occurs, Hills (1966) proposed that a critical volume of gas V_c was released into the tendon and ligamental tissues. A rearrangement of equation [3-A] produces the familiar linear relationship between initial and final pressures, P_i and P_f, respectively, to result in limb pain DCS.

$$P_i = ([V_c/\beta] + 1) P_f \qquad [8A]$$

To produce a nonzero intercept, Hills introduced factors that included surface tension, tissue deformation pressure (Nims, 1951), and a pressure for critical nerve deformation (Inman and Saunders, 1944). Since any gas present in the body would be subjected to small pressures in addition to the ambient, it is necessary to account for them in some manner. This Hills did by replacing P_f in equation [1A] with p_t, the pressure at the tissue level. In the manner in which the equations are derived here, this would be equivalent to the pressure exerted by the weight δ of the piston itself.

$$p_t = P_f + \delta \qquad [9A]$$

For the *in vivo* case, equation [1A] then becomes

$$\beta P_i = \beta (P_f + \delta) + V (P_f + \delta) \qquad [10A]$$

The equation was not meant to explain events other than saturation decompression with a single step. Experimentally, it is known that most of the inert gas remains in solution following decompression (Powell, 1972b, 1973; Powell and Weydig, 1974; Powell, 1977; Powell, Spencer, and von Ramm, 1982; Hills, 1978). Thus, combining equation [5A] with equation [7A] into [10A] produces

$$P_i = \frac{(V_c/\beta) + 1)}{(1- \sigma)(1- \lambda)} [P_f + \delta] \qquad [11A]$$

where σ and λ will vary from zero to unity. Therefore, in a plot of P_i versus P_f—a plot that is employed to illustrate the change of maximum allowable tissue pressure ("M-value") reduction with pressure—the slope will contain the factors

$$m = [1/(1- \sigma)(1 -\lambda)][V_c/\beta] + 1$$

and the y-intercept will be

$$b = \{1/[(1-\sigma)(1-\lambda)](V_c/\beta + 1)\delta$$

This is depicted in figure 2-11.

For "tissues" of varying halftimes, the variation slope can be explained by the increased value of both σ and λ. This simple physicochemical model accords with the "classical" explanation that "fast" tissues can sustain a higher degree of supersaturation and also possess a high perfusion. The data of Bühlmann (1984) indicate that extrapolation of the ascent limiting lines for "tissues" of various halftimes yields intercepts of different values. This can be explained by

(a) the variation in the gas wash-out factors λ and inert gas solubility β,

(b) different degrees of the super-saturation σ, and

(c) the variation in the "critical volume" V_c.

The common notion that "fast" tissues are highly perfused would seem to indicate that the principal cause of increased tolerance of these tissues is the difficulty of reaching a sufficient gas volume V_c in these regions. The treatment presented here indicates that the "long halftime tissue" involved in the development of altitude DCS can be described as one that

(a) has a very small "loss factor", and

(b) does not sustain a high degree of oversaturation.

This latter point means that there is (normally) a relatively high density of micronuclei present and supersaturation is not sustained since some of the dissolved gas can be shunted into these voids.

In reality, it is not a physical requirement that σ and λ remain constant within the tissues during the decompression phase. The smaller the amount of inert gas in physical solution (smaller value of σ), the greater the

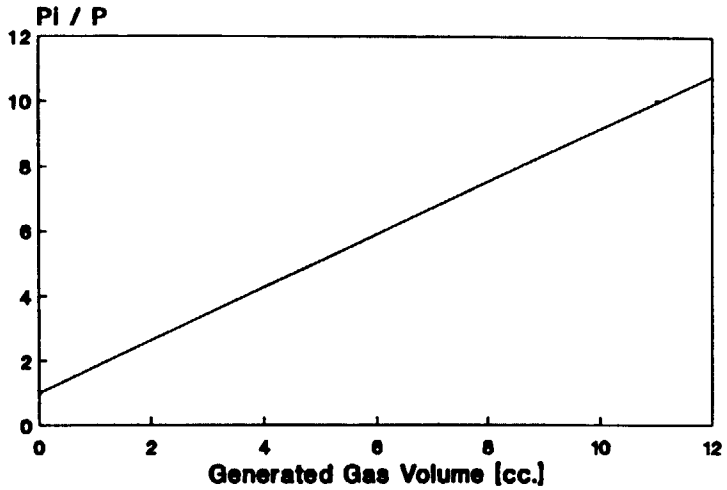


Figure 2-8. Gas volumes created with decompression—no loss or supersaturation.

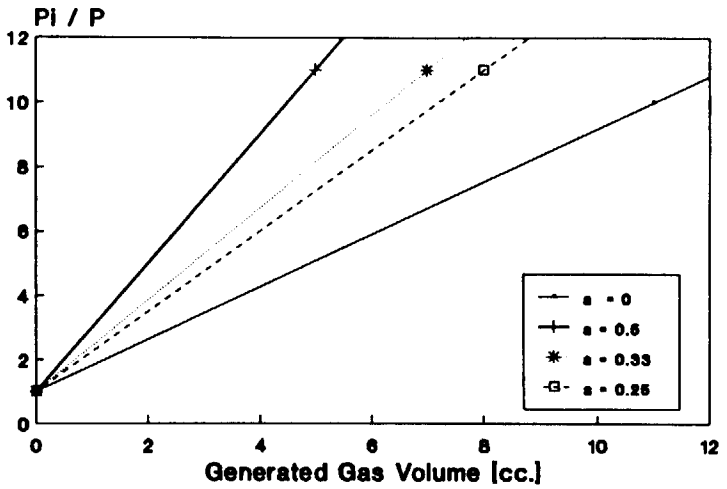


Figure 2-9. Gas volumes created with decompression—case with varying supersaturation.

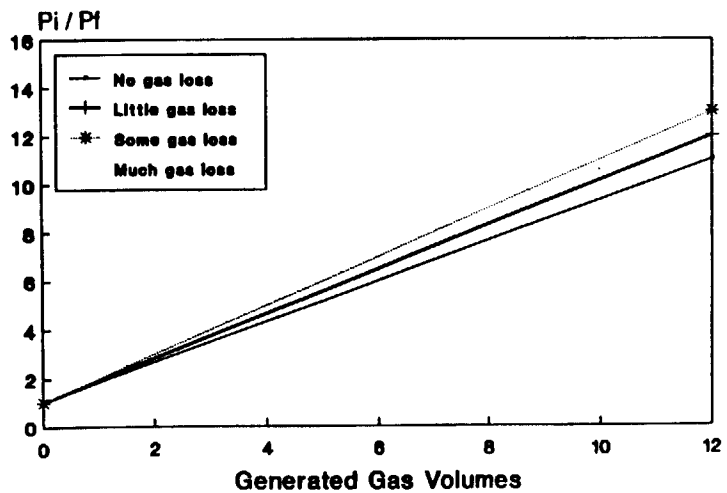


Figure 2-10. Gas volumes created with decompression—case with loss of saturated liquid.

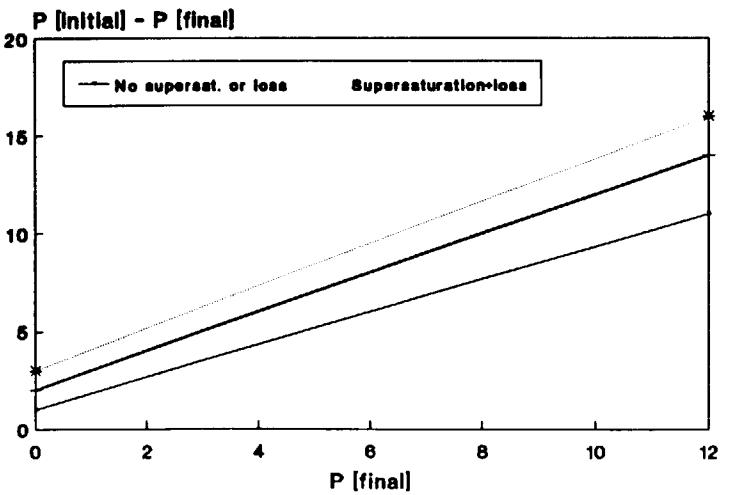


Figure 2-11. Ascent constraint plot—generation of M-values.

volume of tissue gas **V** produced and the smaller the loss of inert gas from the tissue via the blood. We know that, in living systems, two factors will play a role with respect to the development of a tissue gas phase (and subsequent DCS).

(a) If the blood perfusion is not constant within a given decompression period, a considerable degree of temporal inhomogeneity exists. Any variation in the degree of supersaturation will produce a change in the total amount of dissolved gas that can be removed and in the perfusion constant.

(b) The degree of supersaturation is time dependent; that is, $\sigma = f(t)$. Given a sufficient period of time, any supersaturation will disappear.

The total amount of gas that can be released into any microvolume then becomes a function of

(a) The amount of dissolved tissue inert gas taken up during the compression phase. This puts a limit on potential tissue gas volume; and

(b) The amount that actually forms since dissolved inert gas is lost as a consequence of perfusion.

When systems lose varying degrees of dissolved inert gas and varying degrees of supersaturation, curves of the type in figure 2-11 can be generated that have a strong resemblance to the "allowable ascent curves" for tissue with differing halftimes. The **primary variables** in the modified critical volume (or "stoichiometric") model are

(a) The ***degree of supersaturation*** present during decompression in a given "compartment," or microregion, of a tissue; and

(b) The *perfusion*.

From experiment, the degree of supersaturation is known to be generally quite high, probably $\sigma > 0.9$ for the unit gravity case.

It is postulated that the ***primary reason for the mitigation of the signs and symptoms of DCS is a reduction in concentration of tissue gas micronuclei, which are the agents responsible for the loss of supersaturation. These will modify both the volume of gas produced at the tissue level during decompression and the number of moles of gas lost from a microregion during decompression.***

Since dissolved inert gas is lost through perfusion during the decompression phase, the longer the interval between the pressure change and the initiation of gas phase formation, the greater the total volume V can become. The

(a) degree or intensity of the DCS problem(s), and

(b) the percentage of subjects developing problems should be inversely related to the time of onset.

This has been found to be true for altitude DCS (Ferris and Engel, 1952).

The physical basis of the stoichiometric explanation upon which the ARGO experiment was planned postulates that tissue micronuclei are formed more readily in the lower extremities since gravitational forces are exerted most on the these tendons and ligaments as they stretch and contract with the full loads of the body weight on them. Naturally, they are carrying anywhere from 140 to 200 lb for hours every day as individuals walk about. In zero g, while astronauts still perform considerable movement with the lower extremities, the forces on their limbs are considerably reduced since their limbs must counteract inertia only.

Under unit gravity conditions, we imagine the continual formation of tissue micronuclei (fig. 2-12). Stable nuclei probably cannot exist since their existence would imply viscoelastic properties not found in living tissue and/or that the organic "skin" would be impervious to the diffusion of gas. In the latter case, such an entity could not grow by the inward diffusion gas since the boundary would be impermeable. Therefore, there must be a finite lifetime t for the gas micronucleus. Fox and Hertzfeld (1954, appendix) have shown that, with no undersaturation, the dissolution time t for a bubble of radius a and surface tension σ is

$$t = (a^2/3D\alpha)(1 + [p_o a/2\sigma])$$

If we take the case for a gas bubble situated in a collagenous tendon (semi-aqueous tissue) and assume reasonable values for the diffusion coefficient D and solubility of nitrogen (appendix),

$D = 2 \times 10^{-8}$

a = 1 micron	t = 10 minutes
= 5 micra	t = 2.7 hours
= 8 micra	t = 9.9 hours

We might estimate bubble lifetimes are on the order of 8 to 12 hours. When gravitational forces are removed, thus reducing musculoskeletal forces and leaving only inertia, the nuclei formation rate is reduced (here shown as totally eliminated; fig. 2-13). The density of micronuclei is decreased compared to the unit gravity case (fig. 2-14), and fewer micronuclei are present into which dissolved inert gas can diffuse at decompression. There are two competing processes of elimination of dissolved inert gas: (1) by means of capillary flow, or (2) by means of diffusion into gas reservoirs. Further arguments behind the existence of tissue micronuclei can be found in the appendix of this report.

C. Significance of the ARGO Study

We must consider that we have a ***large number of decompressions in space (N = 110)*** with which to compare the results of the ARGO study. The experience of U.S. astronauts alone is considerable and indicates that some "protective" effect is occurring, either from diminished musculoskeletal activity ***prior to*** decompression or, as some Russian scientists have suggested, from the reduction in musculoskeletal activity ***during*** depressurization in the suit. Russian cosmonauts have sustained an even higher TR and have reported good experience. They do not use the same TR with each egress, but they have a ***weighted average value of 1.85.***

The ARGO study attempts to define a possible mechanism and uses the information to ***generate new DCS risk estimates*** since in-suit Doppler measurements are not available. If we had at our disposal the in-suit Doppler bubble grades, the answer of "estimated risk" would appear quite quickly. Lacking these data, we then compare the ARGO results with the ***considerable experience*** of the on-orbit decompressions.

1. Statistical Predictions of DCS Incidence

From data collected in earlier NASA/JSC tests, it is possible to determine the degree of *in vivo* gas phase formation that is released into the venous return and measured by means of precordial Doppler methods. It can be determined that a "gas volume" of 0.303 (calculated as produced by bed-rested test subjects in the ARGO study) would be produced by a TR ($t_{1/2}$ = 360) of 1.27 (by subjects in unit gravity).

[An estimate based on the number of subjects with Doppler-detectable bubbles allows us to calculate that, in our population, to effect this in the 360-minute compartment would require 175 minutes of oxygen prebreathe by our bed-rested subjects. Similarly, to create an apparent TR of 1.3 in the 360-minute compartment, during the

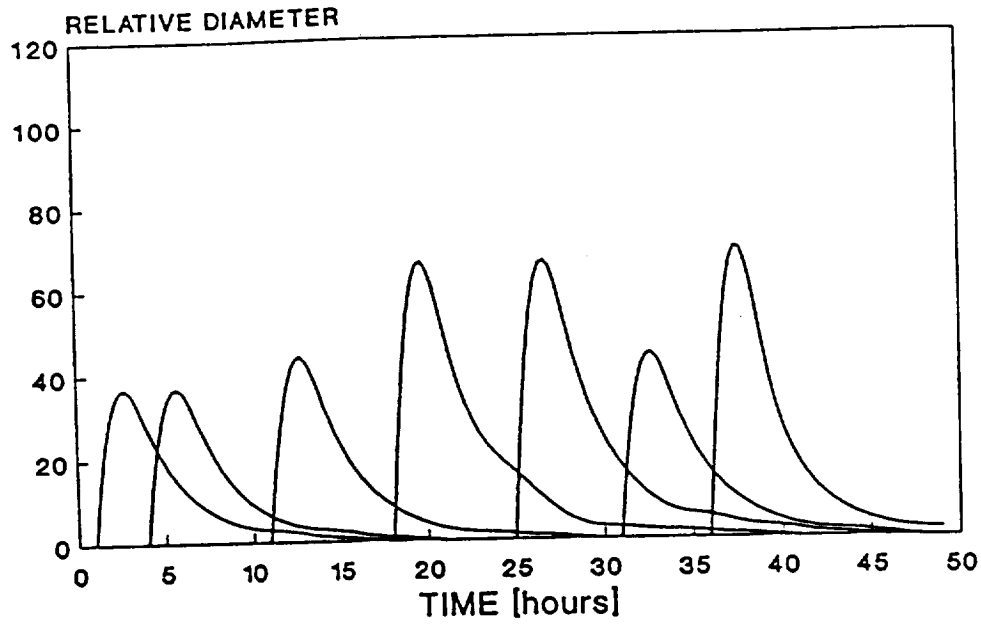
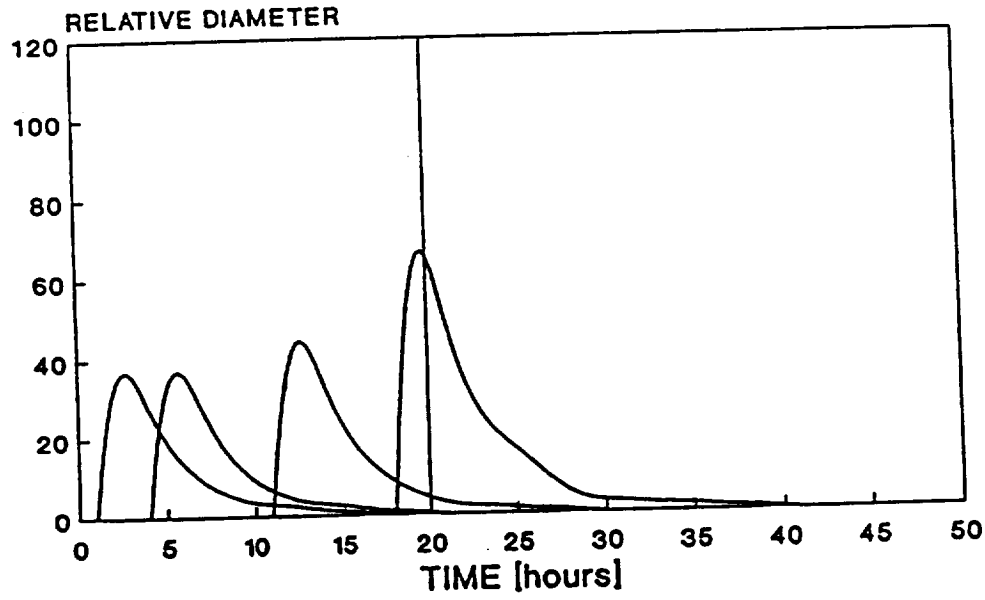


Figure 2-12. Generation and decay of tissue gas micronuclei.



20 Hours, Bedrest Begins -

Figure 2-13. Generation and decay of tissue gas micronuclei.

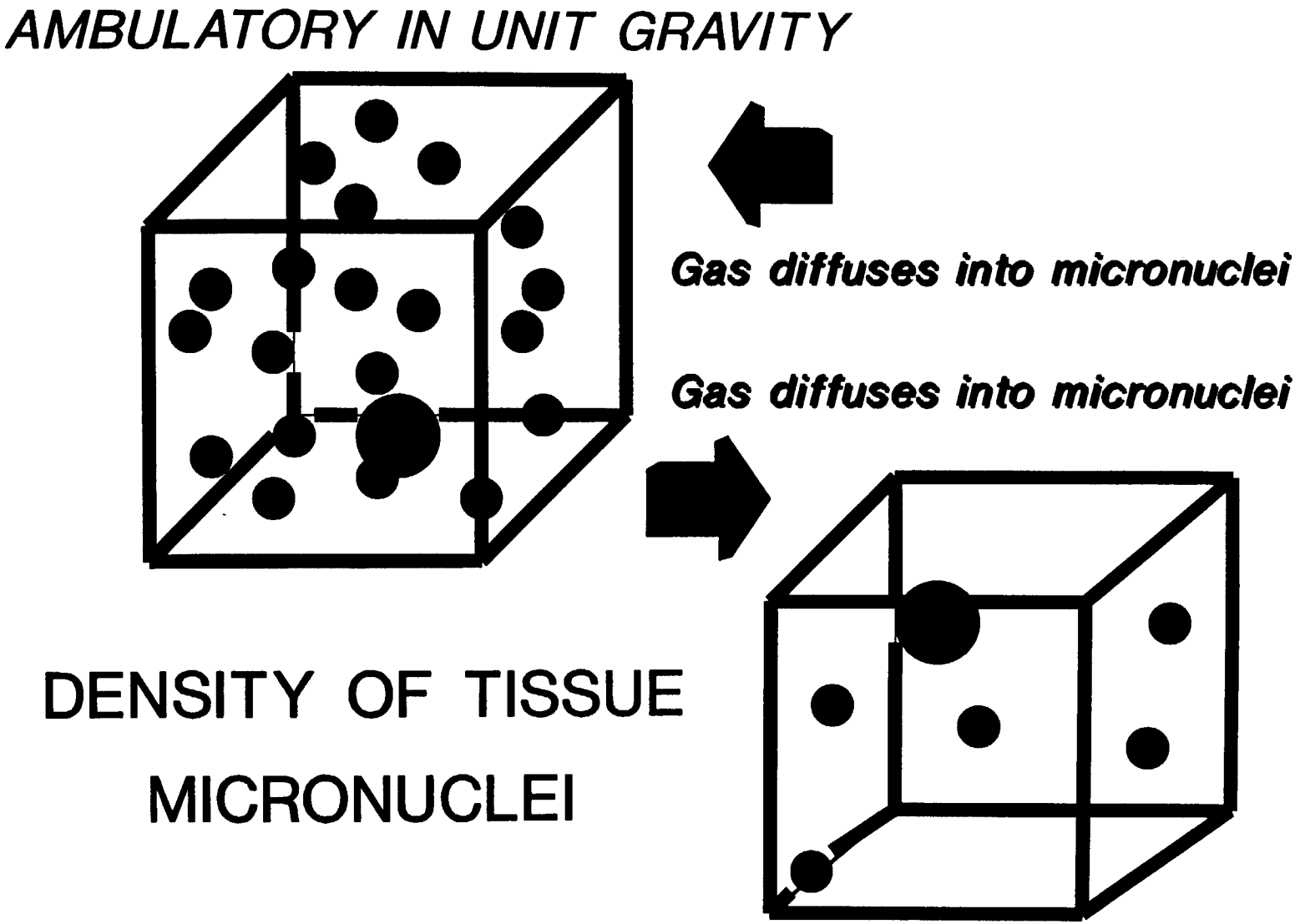


Figure 2-14. Reduced stress in microgravity.

40-minute oxygen prebreathe it would have needed to act as if it were off gassing like a 76-minute compartment. This would have required a 4.8 times increase in blood flow as is calculated by

$$t_{1/2} = \ln 2/\{Q(\alpha_b/\alpha_t)\}$$

an increase in cardiac output and peripheral blood flow in zero g that does not seem to be justifiable to assume].

From Conkin et al. (1987), that ratio (1.27) would produce an incidence of mild DCS of:

$$\%DCS = [TR_{360} - 0.78]^{4.24}/[(TR_{360} - 0.78)^{4.24} + 2.16] \times 100$$

$$DCS = 2.4\%$$

The probability of *not* encountering minor problems of DCS in 37 decompressions is calculated from the binomial theorem

$$f(x) = {}^{n}C_x\, p^x\, (1-p)^{n-x} \quad \text{for } x = 1,2,...,n,$$

(calculated incidence = 2.4%) as 41%. If we enter the Russian experience (and credit the same success probability), we have a combined total of 110 EVAs and a probability of successful completion of all missions of 6.9%. A similar calculation (Conkin et al., 1987) for severe DCS (joint discomfort sufficient to cause an abort of the altitude chamber test) gives from

$$\%DCS = [TR_{360} - 0.78]^{2.50}/[(TR_{360} - 0.78)^{2.50} + 17.61] \times 100$$

$$DCS = 0.98\%$$

The probabilities of *not* encountering severe DCS in the U.S. and the combined U.S./Russian experience are, respectively, 69% and 34%.

We would expect that results consistent with the hypothesis would be indicated by a reduction in the amount of Doppler-detectable gas bubbles indicative of a reduction in tissue gas phase formation and its correlative, DCS. From NASA/JSC ground-based studies, the historical incidence of Doppler-detectable circulating microbubbles (CMB) with ambulatory subjects was 57% for the TR imposed. Of this 57%, the percentage of subjects presenting Grade III or IV bubbles is 86%. Of the ambulatory subjects in this study, 50% exhibited CMB; 100% were of Grades III or IV.

Statistically, we could expect a zero incidence (at the p = 0.95 level) of all, even *minor*, problems of DCS if the true incidence of minor DCS in both ground-based and microgravity environments were equal to 0.2%. This clearly is considerably less than the 20% encountered at NASA/JSC or the 2.4% predicted for this "effective" TR. A predicted incidence of DCS of 0.2% would have an associated (predicted; cf. Conkin et al., 1987) TR [in the compartment $t_{1/2}$ = 360] of 1.06 as determined from

$$TR = [2.16\,(DCS)/(1 - (DCS)]^{1/4.24} + 0.78$$

From Conkin et al. 1987), we have

$$\%\ \text{Subjects c. Bubbles} = (TR - 0.78)^{3.08}/[(TR - 0.78)^{3.08} + 0.47]$$

from which we can calculate, for TR = 1.06, a predicted incidence of subjects with any Spencer Grade of Doppler-detectable gas bubbles of 4.8%.

This "predicted incidence" of DCS (0.2%) on orbit is equivalent to a calculated Doppler "gas volume" of 0.03 [cc.] and is smaller than that determined from the bed-rested test subjects in our ARGO series.

2. Departures from Expectation

The production of an *in vivo* gas phase (measured with Doppler ultrasound) is larger than that predicted for decompression for orbital EVA assuming a < 0.2% incidence of DCS in these activities. Several possibilities arise to explain this.

(a) Some cases of mild joint pain DCS are unnoted by the EVA astronauts, possibly because of the confinement of the pressure suit; or

(b) Other additional mechanisms play a role in the reduction of DCS incidence on orbit such as reduced activity of the subject's lower limbs while decompressed and in the suit (possibly the limb-flex maneuvers used to provoke the release of gas bubbles in laboratory tests themselves generated some of the CMB); or,

(c) Our test sample is small and contains individuals ("outliers") whose capacity for the generation of an *in vivo* gas phase is excessive compared to the norm.

Regarding (c), one such individual (*LD*) was present. He has participated in several NASA/JSC altitude decompressions and his Spencer precordial Grades and their duration are always (Grade IV/4 decompressions) beyond expectation for the group. Such individuals have been noted before in Doppler decompression studies and the phenomenon is well known, although unexplained (Nishi et al., 1980; Powell, Fust, and Thoma, 1982). If we screen out this individual and assume the formation of the gas phase is similar in mechanism, whether there are few or many micronuclei, it is possible to estimate (from a curve with parallel slope to the unit gravity case) that the "gas volume" is reduced for this adjusted group. Then the expected incidence of mild DCS from our group is approximately 1% and the incidence of severe DCS from our group is on the order of 0.4%.

3. Estimations of NASA DCS Risk

To give an idea of the utility of this study, some *estimates* are given. Eliminating the influence of "LD" by screening him from the Doppler data allows the estimation (as determined by the remaining test subjects in the series) for isolated prebreathe (i.e., no prior reduction of the Shuttle to 10.2 psi) prior to egress for EVA. For example, a prebreathe time of 90 minutes would yield a $TR_{[360]}$ of 2.25 and an estimated incidence of mild and severe DCS of 16% and 3%, respectively. For 2 hours, we would get a $TR_{[360]}$ of 2.12 and a mild and severe incidence of 7% and 1.5%, respectively. (All ***estimates*** are based on the revised predictions of Hallum (1990) from logistic models of NASA data.)

Part III.

Neurologic Decompression Sickness: Transcranial Doppler Ultrasound Monitoring During Hypobaric Decompression

Summary

1. Several bed-rested subjects produced gas bubbles in the venous return and the right side of the heart. These subjects would be susceptible to neurologic DCS from right-to-left shunts, either cardiac or pulmonary.

2. Two out of three individuals (one ambulatory, the other bed rested) with atrial septal defects and gas bubbles developed either frank neurologic DCS or an unexpected response to decompression (viz, skin mottling and orthostatic intolerance).

3. These neurologic involvements are serious problems, and the need for recompression facilities on orbit cannot be eliminated by the ARGO study.

I. INTRODUCTION

A. Decompression Sickness

1. Manifestations

Depending upon (a) the site of gas phase growth in the tissues or (b) migration of bubbles by the bloodstream, DCS can manifest itself in many forms. The forms generally include the following, although the listing is not complete. For example, lymphatic obstruction is missing.

(a) Neurologic DCS from the formation of gas bubbles in the brain or spinal cord or from the gas embolization of the brain or cord.

(b) Joint pain DCS from the formation of a gas phase in the connective tissue (tendons, ligaments) of joints.

(c) "The chokes" from the accumulation of gas bubbles in the pulmonary vasculature.

(d) "Skin bends" and pruritis from the formation of gas bubbles (purportedly) in the capillaries of the skin.

(e) The "staggers" from the formation of a gas phase in the cerebellum, the VIIIth cranial nerve or the organs of balance.

(f) Cardiovascular collapse from the appearance of a very large gas bubble load in the right heart leading to a great reduction in cardiac output.

(g) Dysbaric osteonecrosis from the [attributed] presence of a gas phase in bone.

2. NASA Interest In Cerebral Gas Bubbles

In this portion of our Technical Memorandum, we will describe the results of a study by NASA concerning the role of gas bubbles generated during decompression to altitude, a process that is a part of EVA. As a

portion of this work, provisions were initially made for the detection of (a) decompression gas bubbles in the arterial circulation of subjects, and (b) screening for the presence of a patent atrial septal defect by means of B-mode ultrasound and saline contrast echocardiography. It was decided that, if screening were performed predecompression, individuals with a patency would not be excluded since

(a) Some investigators find no relationship between patency and an increased incidence in neurologic DCS in a population of scuba divers. Wilmshurst et al. (1990) found a prevalency of patent right-to-left shunts of 25% (26/105) in a subgroup that never experienced DCS versus a prevalence of 24% (8/34) in a group that experienced late neurologic DCS and 15% (3/20) for joint pain DCS.

(b) There is no indication that (approximately) 25% of test subjects with numerous decompression gas bubbles (e.g., Spencer Grade IV) develop central nervous system (CNS) DCS or peripheral nerve involvement. This would be expected since the prevalence of PFOs determined in a population postmortem is ≈ 20% to 30%

(c) The presence of a PFO is not considered exclusionary since astronauts are not (currently) eliminated because of such a right-to-left shunt.

Clinically, the determination of a PFO requires intravenous injection of air microbubbles during a provocation or augmentation maneuver (following exhalation from a Valsalva) and an echocardiograph. If bubbles are not detected in the left ventricle by means of a transthoracic imaging device, many practitioners elect to use a transesophageal imager, which is a noxious test for the patient. It has been suggested that one way to increase sensitivity is to detect air bubbles in the ascending aorta (suprasternal notch) or in the MCA (very high signal-to-noise ratio), both by means of range-gated Doppler.

In the course of both saline contrast injections and hypobaric decompressions, the following were assessed:

(a) Detection of gas bubbles in the pulmonary arteries, and/or

(b) Detection of gas bubbles in the MCA (and possibly in the ascending aorta).

B. Background Hypothesis: Cerebral Gas Bubbles

Inert gas bubbles that possess a radius of less than 50 microns have their genesis in tissue capillaries during decompression and are then released during muscle contraction into the central venous return. As a consequence of their small diameter, these inert gas bubbles may not be completely sequestered by the pulmonary vascular filter. Questions concerning these gas bubbles are

(a) If present, could they represent a potential source of emboli and act as causative agents of subtle neurologic lesions in astronauts during EVA?

(b) If present, could these inert gas microemboli be detected easily and noninvasively in the MCA of human subjects by using transcranial Doppler ultrasonography?

C. Pulmonary Gas Embolism and Arterialization

The possibility of bubbles of inert gas being generated within or entering into the systemic arteries and embolizing the central nervous system (CNS) (Type II DCS) has always presented a serious difficulty whenever a change of ambient pressure is

experienced. These gas bubbles may result from

(a) *De novo* genesis in the arteries (Brubakk et al., 1981),

(b) Release from supersaturated tissues into the venous return with subsequent transpulmonary transport (Emerson et al., 1967; Powell, 1977),

(c) Rupture of small airways (Waite et al., 1967).

Numerous studies have investigated the question of pulmonary gas embolism over the years; however, these investigations have treated the situation where the gas bubbles in the vena cava have been large (approximately 0.1 to 1 mm in radius) (Durant et al., 1947; Spencer and Oyama, 1971; Powell and Johanson, 1978; Powell et al., 1982). Mechanisms for passage to the arterial system have been recognized for many years. They include normal and well-defined anatomical shunts such as pulmonary arteriovenous anastomoses, bronchial venous shunts, large pleural capillaries (Catchpole and Gersch, 1947; Haymaker and Johnson, 1955; Malette et al., 1962; Wittmer, 1962), and pathologies such as PFO.

Under conditions normally encountered in lung capillaries, Hills and Butler (1981) state that the surface tension of gas bubbles should be less than the "physiologic" value of 50 dynes/cm^2. This large value for surface tension yields a retarding pressure of 150 torr for a bubble of 5 micra. A reduction of surface tension to 2 dyne/cm^2 can be produced by dipalmitoyl lecithin (DPL), which is a normally present lung surfactant. DPL can also induce a contact angle of up to 70°, thus reducing the retarding pressure to approximately 3 torr.

Powell and Spencer (1981) reported that when gas was introduced into the venous return of sheep—*not by means of a catheter that would generate large gas bubbles* (> 0.1 mm radius) but, rather, by means of *small gas bubbles spawned in tissues following decompression* (with the creation of microbubbles)—the results were surprisingly different. In this latter case, "arterialization," or the passage of gas bubbles from the venous circulation into the systemic arterial circulation, was *not uncommon* even in the *absence of an elevation of the RVSP* [right ventricular systolic pressure].

D. Central Nervous System (CNS) DCS

In general, CNS involvement in DCS was considered to be low. Other studies indicated a greater degree of involvement, however. A number of studies (Kelly and Peters, 1975; Levin, 1975; Peters et al., 1977) indicated that neurologic and psychologic problems exist following CNS DCS. In order of frequency, the problems noted were: personality change, headache, recent memory impairment, discoordination, paresthesia and weakness, hearing loss, vertigo, urinary symptoms, and dysphasia. Impaired divers also demonstrated low scores on verbal and nonverbal portions of the Wechsler Adult Intelligence Scale. The manner in which the subjects were divided between test and control makes this study less than ideal, however.

Deep-sea divers report a high incidence of subtle, subjective complaints with DCS among which are: lethargy, confusion and mental cloudiness, and a general perception that all is not well, which may indicate cerebral involvement. Many of these symptoms have also been experienced by individuals who have undergone a safe decompression and who have *not* experienced what classically would be called frank DCS. The Principal Investigator [Michael R. Powell, Ph. D.] is included in this group.

E. Neurologic Sequelae

The presence of detectable gas bubbles in the MCA is not *prima facie* evidence that neurologic damage is occurring. Possible untoward events could be mitigated by several factors.

1. The presence of numerous overlapping collaterals would serve to protect brain tissue from anoxia if embolism was not extensive.

2. The gas bubbles are composed primarily of oxygen and would dissolve and be metabolically consumed by the tissues of the brain even if they were able to embolize the capillaries. Arterial gas emboli that appeared in the early portion of decompression, when the brain is not yet denitrogenated, would be considered to be the most pathogenic from a neurologic position.

3. Numerous air bubbles have been detected by means of surgically implanted Doppler ultrasound probes placed around the carotid artery of sheep (Powell and Spencer, 1981). These subjects rarely demonstrated evidence of neurologic damage.

4. Spencer (1990) and Powell (unpublished observations) noted both gaseous and formed element emboli in the MCA while monitoring with the transcranial Doppler (TCD) during surgery. Spencer reports that a postoperative analysis of 100 TCD monitorings demonstrated gaseous emboli in 44 patients and formed element emboli in 11 patients. Only one patient gave evidence of postoperative stroke; the bubble emboli were detected for 14 sec in this individual. Two patients with extensive formed-element emboli sustained severe postoperative strokes.

5. Last, we might consider historical evidence. Human subjects have used these profiles in the past with no obvious evidence of CNS involvement. If gas bubbles are detected in the MCA, however, it would be prudent to consider initiating a program of psychometric testing as has been done with deep-sea divers (Vaernes et al., 1989).

F. Transcranial Doppler (TCD) Ultrasonography and Bubble Detection

Aaslid et al. (1982) discovered that the vessels of the brain could be interrogated noninvasively by means of Doppler ultrasound. Placement of a hand-held probe over the temporal region of the skull will position the probe over a relatively thin region of osseous tissue. With proper angulation, an ultrasound beam can be made to insonate the major blood vessels of the brain, including the deep-lying circle of Willis.

The blood vessel that is the easiest to locate and is most utilized for intracranial hemodynamic monitoring is the MCA (fig. 3-1). Gas bubbles present in the MCA produce very intense reflections of the transmitted ultrasound signal superimposed upon the normal blood flow signal. Bubbles that may have escaped the pulmonary filter could be detected with ease as either discrete reflections (Aaslid and Lindegaard, 1986; Spencer 1990) or from an increase in Doppler signal intensity (Ries et al., 1989).

Gas bubbles of a radius equal to or greater than 50 microns are expected to give discrete reflections. Gas bubbles smaller than 50 microns could be expected to reveal their presence by a modification of the pattern of blood flow.

The amplitude of the reflected Doppler ultrasound beam is a function of the difference in acoustic impedance between the conducting medium (serum) and the individual scattering sites. This difference is modest for erythrocytes, but it is compensated for by their large numbers. The difference between the acoustic impedance of gas bubbles and serum is very high. This difference will produce an

increase in the returned signal intensity even when discrete, individual bubbles are not detectable.

II. EXPERIMENTAL METHODS

1. Monitoring for venous return gas phase formation was performed precordially with a commercially available 2 MHz pulsed (or continuous wave, depending on the subjects) Doppler ultrasound device (*Transpect*, MedaSonics, Fremont, CA). Standard precordial Doppler ultrasound techniques (Powell et al., 1982) were used that are similar to those employed at NASA/JSC in previous hypobaric trials (Conkin et al., 1987).

2. To monitor for the presence of cerebral gas microemboli, a 2 MHz pulsed Doppler ultrasound device was employed (*Transpect*, MedaSonics, Fremont, CA). The MCA was identified on the basis of:

   (a) The anatomic position of the transducer,

   (b) The depth of the vessel as determined by range gating, and

   (c) Characteristics of the blood flow signal (Fujioka et al., 1989). Suitable transcranial Doppler signals were obtained through the temporal bone "windows" (thin regions; fig. 3-2) of subjects prior to signal entrance into the hypobaric chamber. Hand-held positioning of the ultrasound transducer was done.

3. Flow signals in the MCA were expected to be free of gas bubbles when the subjects were resting. These signals were processed by the *Transpect* to yield an FFT signal (fig. 3-3), and this signal was routinely viewed during the chamber study. An amplitude histogram could also be generated by *Spectro*, a public domain software (shareware) program on the NeXT computer (fig. 3-4). Upon flexure of a joint, showers of gas bubbles were detected in the pulmonary artery by means of a precordial Doppler bubble detector in some subjects. These same individuals were checked for the presence of bubbles in the MCA following joint flexure.

4. Gas bubbles in the MCA with a radius equal to or greater than approximately 50 micra were expected to give discrete acoustic reflections (Spencer, 1990; Powell, unpublished observations). Spencer describes these as

   (a) Transient, less than 0.1 sec in duration depending on their position in the velocity/frequency FFT spectrum;

   (b) Random in position in the cardiac cycle;

   (c) Greater than 6 dB above the background Doppler flow signal; and

   (d) Unidirectional.

   While we have not yet definitely noted small bubbles in the MCA, it could be proposed that smaller gas bubbles could be expected to reveal their presence by an increase in the reflectance of the Doppler signal. This would be seen as the brightening of the FFT on the instrument screen (Chimowitz et al., 1991). In retrospect, it is believed that this occurred with subject WF.

5. Saline contrast echocardiography was performed by rapidly drawing the fluid back and forth between two syringes in tandem following the addition of a small volume of air (to fill the syringe hub). This fluid was then injected in a bolus through a catheter placed into the antecubital vein. The subject was supine and breathing normally while the echocardiograph screen was observed for the presence of bubbles. If bubbles appeared in the left heart, the indication

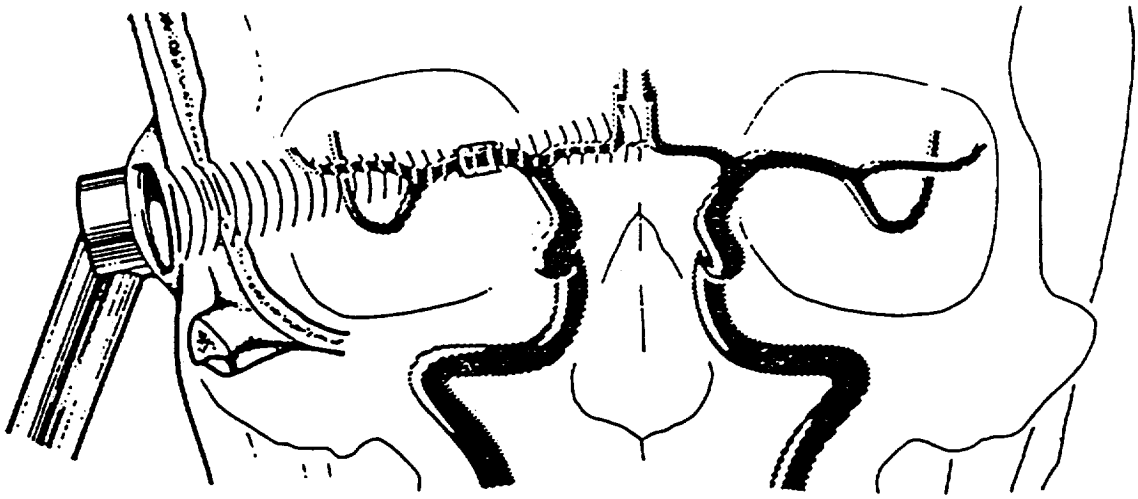


Figure 3-1. Frontal view of the ultrasound probe directed toward the MCA. The cylinder around the MCA indicates the observation region (sampling volume for Doppler recording. the distance from the middle of the cylinder to the probe corresponds to the depth setting.

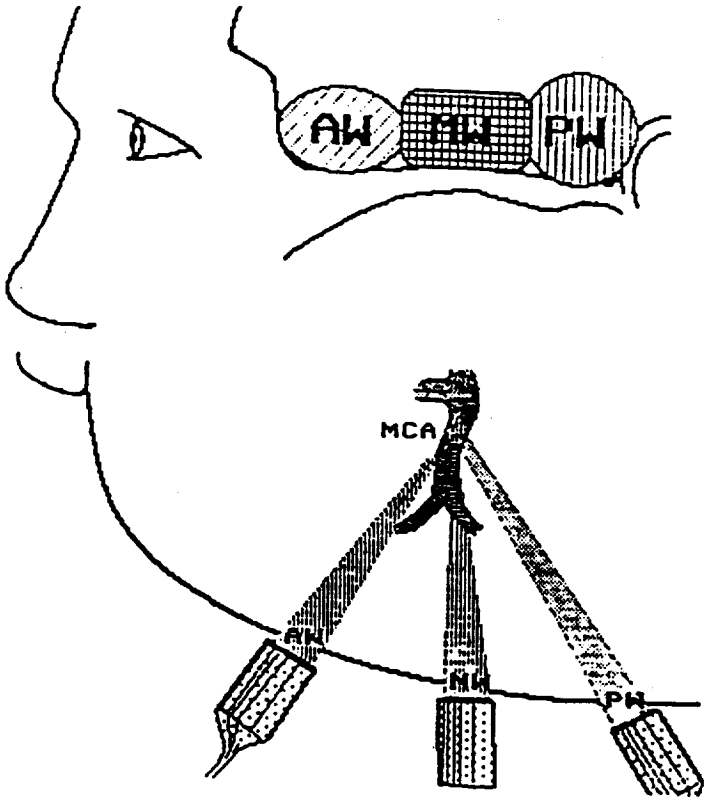


Figure 3-2. Transcranial Doppler signals obtained through temporal bone "windows."

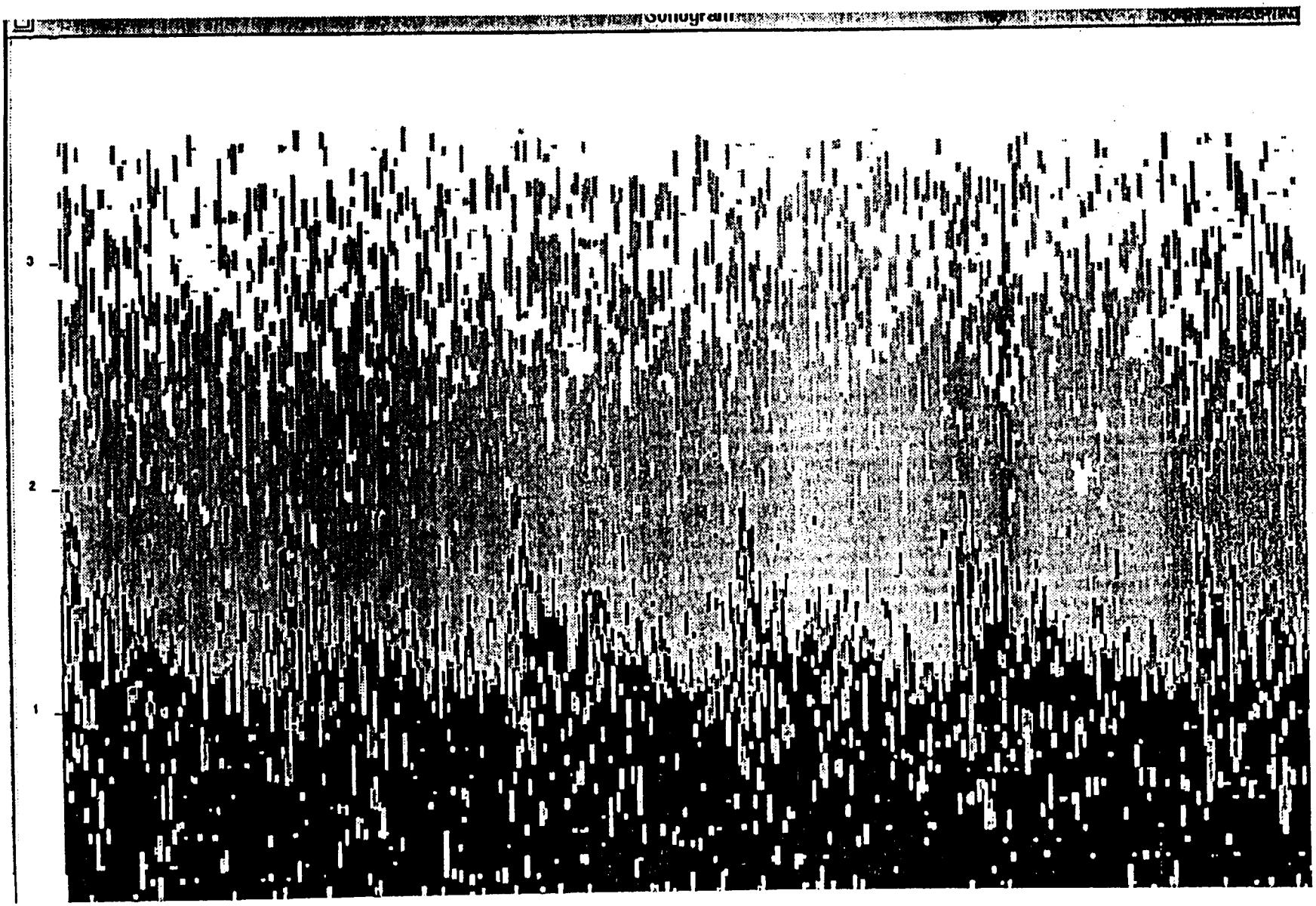


Figure 3-3. Signals processed by the Transpect to yield an FFT signal.

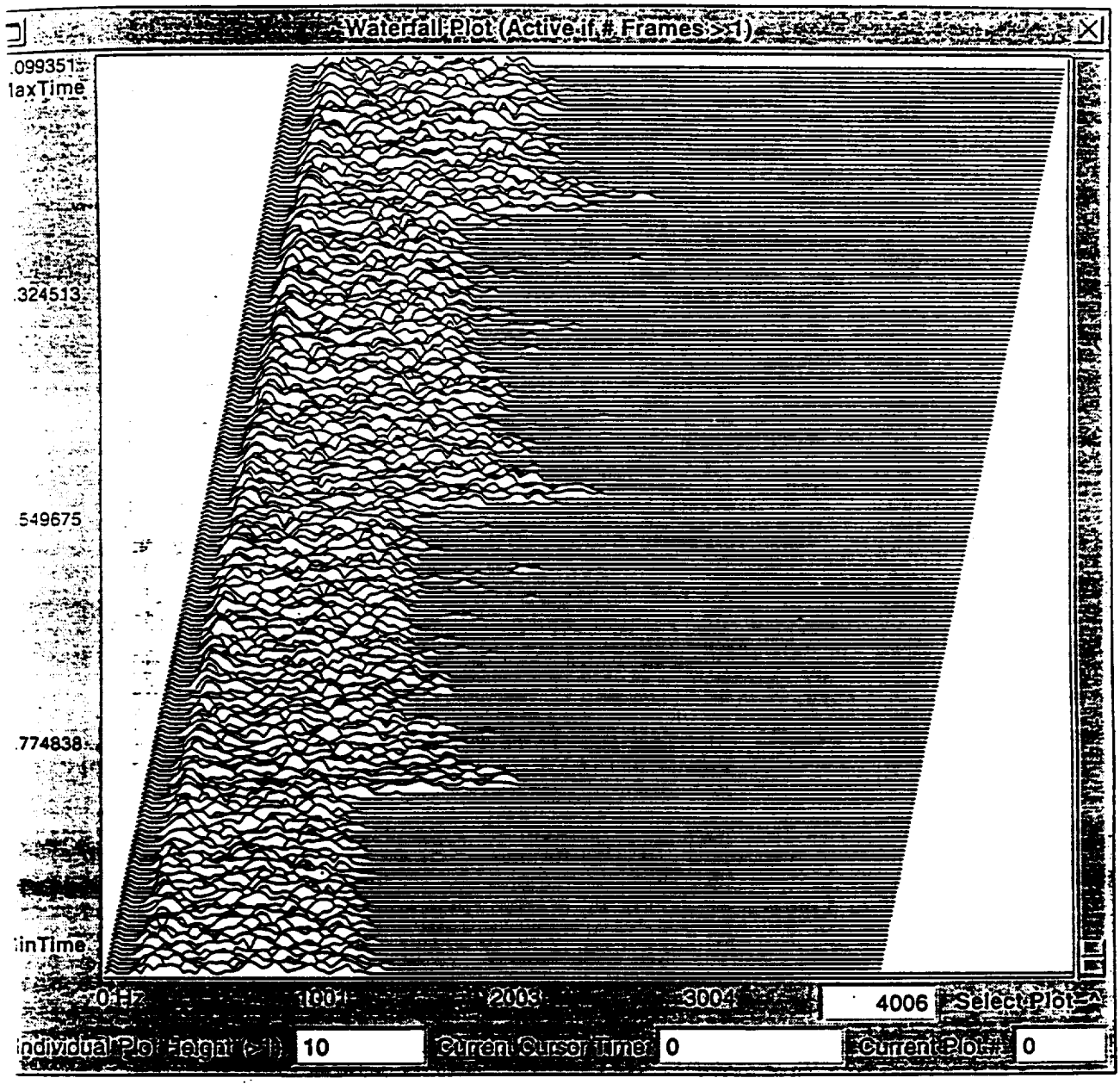


Figure 3-4. Amplitude histogram generated by Spectro.

of a "spontaneous" or "resting" defect in the interatrial septum was noted. In the absence of gas bubbles in the left ventricle, a provocation or augmentation maneuver was then performed (Valsalva) wherein the contrast agent was injected as the subject bore down and immediately exhaled. This method is standard and successful in detecting septal defects (Teague and Sharma, 1991; Lin et al., 1992; Chimowitz et al., 1991).

III. RESULTS

A. Gas Bubbles in the MCA Circulation

The majority of individuals with even numerous gas bubbles present in the right heart did not have ultrasonically detectable gas bubbles in the arterial circulation.

The number of individuals with neurologic DCS (Type II), which presumably came from arterial gas bubbles, is approximately what would have been expected from the results of Powell and Spencer (1981) with Doppler-monitored sheep. During 86 decompressions in which the sheep displayed Spencer precordial Grade III or higher, bubbles were detected in the carotid artery in 7% of the subjects displaying Grade IV precordial bubbles and in 50% of the subjects with Grade IV+. It is not known if IV+ is realistically attained in humans under normal conditions. Amongst our subjects, 13 had Grade III or higher, 1 had distinct arterial bubbles (=8%), while the second WF had a "brightening" or intensification of the FFT Doppler signal that would indicate literally tens of thousands of microbubbles (d < 5 micra). The 8% figure is similar to the earlier findings with sheep, but there is no particular reason to believe that the findings on sheep would be similar to those on humans.

Of the three people with resting PFOs, two experienced Spencer Grade IV bubbles. One individual (WB) had arterialization and neurologic symptoms. The other (KA) did not give any evidence of right-to-left shunting and arterialization, either by insonation of the left ventricular outflow tract or with the TCD. This included both the detection of individual gas bubbles and the FFT amplitude increase from temporally nonresolved microbubbles. The third (WF) probably had many microbubbles of a different nature than those described by the general Spencer code. This individual displayed postural instability and an abdominal rash following decompression, which continued for some hours after repressurization. WF received hyperbaric oxygen therapy (U.S. Navy Table 6).

It is extremely important to recognize that, while the incidence of precordial bubbles was reduced considerably in bed-rested subjects, the incidence was <u>not</u> reduced to zero. These individuals are at risk for neurological DCS secondary to right-to-left shunting through cardiac or pulmonary routes. Two out of three of the subjects with defects in the interatrial septum displayed a response to decompression that is not considered normal.

The requirement for treatment of neurologic DCS in microgravity remains unchanged until such time that its etiology is better characterized and its risk is reduced.

The summary of Doppler test results from the NASA studies are given in table 3-I.

B. Number of Gas Bubbles in the Right Heart

The maximum number of gas bubbles in the right heart during decompression is not known, although an estimate can be made.

<u>1. Gas Loads Following Decompression</u>

Powell and Spencer (1981) determined the gas content of a Spencer precordial Doppler Grade IV from steady-state infusions of gas through a capillary into sheep and by additional diving experiments.

Table 3-I. Summary of Doppler Test Results

NAME	MAXIMUM DOPPLER GRADE AMBULATORY	MAXIMUM DOPPLER GRADE BED RESTED	TCD BUBBLES AMB.	TCD BUBBLES BED REST	SALINE CONTRAST ECHOCARDIOGRAPHY
1. GH	0 (1)	0 (7)	.	.	NO ARTERIALIZATION
2. KW	III (6)	0 (2)	.	.	Lost to follow-up
3. DM	III (2)	0 (4)	0	.	NO ARTERIALIZATION
4. LD	IV (15)	IV (3)	0	0	NO ARTERIALIZATION
5. BH	0 (3)	0 (10)	0	.	Not tested
6. SB	III (4)	II (5)	0	0	NO ARTERIALIZATION
7. DB	0 (5)	0 (6)	.	.	Not tested
8. WB	IV (7)	Withdrawn from study	+	.	**Resting** ARTERIALIZATION
9. SB	IV (11)	0 (8)	0	.	NO ARTERIALIZATION
10. KH	0 (8)	Lost to follow-up	.	.	Not tested
11. CK	0 (10)	0 (9)	.	.	NO ARTERIALIZATION
12. DS	0 (9)	Lost to follow-up	0	.	Not tested
13. DF	III (13)	II (12)	.	0	NO ARTERIALIZATION
14. PL	IV (12)	0 (13)	0	.	NO ARTERIALIZATION
15. JS	Lost	0 (14)	.	.	Not tested
16. KG	0 (14)	0 (11)	.	.	Not tested
17. TJ	0 (19)	0 (15)	.	.	Not tested
18. KC	0 (19)	0 (16)	.	.	Not tested
19. TO	0 (16)	Lost to follow-up	.	.	Not tested
20. WH	III (21)	III (17)	.	0	NO ARTERIALIZATION
21. WF	Withdrawn	"0" (18)	.	.	**Resting** ARTERIALIZATION
22. CA	0 (18)	0 (23	.	.	Not tested
23. MS	IV (20)	0 (22)	.	.	Not tested
24. KA	IV (22)	0 (20)	0	.	**Resting** ARTERIALIZATION
25. DK	IV (24)	II (21)	0	0	NO ARTERIALIZATION
26. JA	0 (23)	0 (24)	.	.	Not tested
27. LD	Withdrawn from the study				**Resting** ARTERIALIZATION

SUMMARY:	Precordial Grades		TCD Bubbles/Subjects:	With Resting PFO
	0 = 12	0 = 17	0/2	
	I = 0	I = 0	---	
	II = 0	II = 3	0/3	
	III = 5	III = 1	0/3	
	IV = 7	IV = 1	1/6	1/2
Bubbles found:	12/24 individ.	5/22 individ.		

Resting R-L Shunts = 4/14 = 28%

$$beat V_{decomp} \approx 2.5 \times 10^{-2} \text{ [cc./kg/min]} \times 50 \text{ [kg]} / 80 \text{ [beats/min]}$$

$$beat V_{decomp} \approx 1.6 \times 10^{-2} \text{ [cc./beat]}$$

2. Gas Loads Upon Contrast Injection

These gas volume estimates are derived from the work of Keller et al. (1987) and Sanders et al. (1991) where they estimate the radius of air-filled microbubbles at 3 micra. We can thus calculate

$$V = [4/3]\pi r^3$$

$$V_{microbubble} \approx 1 \times 10^{-10} \text{ [cc./bubble]}$$

Keller et al. (1987) and Sanders et al. estimate that, for full opacification of the right ventricle upon B-mode visualization in all subjects injected, 0.04 [cc. injectate/kg] of fluid containing 4×10^8 [air-filled microspheres/cc. injectate] is required. This would then approximately correspond to the B-mode opacification (or be somewhat greater) seen upon visualization during decompression.

$$V_{microbub} \approx 1 \times 10^{-10} \text{ [cc. air/bubb.]} \times 4 \times 10^8 \text{ [bubbles/cc. inject.]} \times 4 \times 10^{-2} \text{ [cc. inject./kg]} \times 80 \text{ [kg]}$$

$$V_{microbub} \approx 12.8 \times 10^{-2} \text{ [cc.]}$$

which appear over approximately 5 heartbeats. Thus,

$$V_{microbub} \approx 12.8 \times 10^{-2} \text{ [cc.]}/5 \text{ [beats]}$$

$$beat V_{microbub} \approx 2.6 \times 10^{-2} \text{ [cc/beat]}$$

The injected microspheres (microbubbles) and the decompression bubbles (for a Grade IV) are thus approximately equal in volume, although it appears that more gas is contained in the microspheres. This might account for arterialization more often by the injection method.

IV. DISCUSSION

A. *Earlier Studies*

During air injection experiments (per catheter into the jugular vein of sheep) when bubbles with large radii r (= 100-300 micra) serve as the pulmonary embolizing agent, gas bubbles are not detected by perivascular Doppler cuffs on the carotid artery when RVSP is less than 150% of pre-injection control (Powell et al., 1980). In studies to achieve these steady-state pressure elevations, air injections were conducted for 10 to 20 minutes. In cases where small microbubbles were infused (r = 10 to 90 micra) for short injection periods ($t \leq 2$ minutes), Doppler-detectable gas was again not found on the systemic arterial side (Butler and Hills, 1979). We could conjecture that the combination of a small radius in conjunction with an elevation of pulmonary artery pressure acts in concert to effect arterialization. Both conditions are necessary and neither alone is found to be sufficient. The very smallest bubble ($r < 5$ micra) might be expected to dissolve during transpulmonary passage (Meltzer et al., 1980).

A singular contribution of Doppler ultrasonic bubble detectors to our field is the demonstration that bubbles can appear copiously in the central venous return but only rarely in the arterial system. Studies on gas separation in two highly perfused organs—the kidney and the brain—have indicated that these tissues do not readily produce a gas phase following decompression, even when rather aggressive efforts are undertaken to induce one (Powell and Spencer, 1980). Thus, a highly perfused tissue, such as the brain, seems to be resistant to gas phase formation in all but the severest cases of decompression. Neurologic DCS in the brain could have an origin in arterial gas embolism.

The question of transpulmonic passage of the gas phase was first investigated in rats by Emerson, Hempleman, and Lentle (1967). Their work indicated that a gas phase could not readily pass the pulmonary barrier under

normal physiological conditions. Similar studies by Powell (1970) with rats indicated that arterial bubbles could be found in those subjects that expired, although not all rats with arterial bubbles would necessarily die. Furthermore, the majority of these animal subjects showed no evidence of systemic arterial bubbles following decompression on profiles known to result only in limb-bend DCS.

Since venous bubbles appear first, it is logical to assume that the source of arterial bubbles is the pulmonary vasculature. It should be stressed here that, in situations where the vena cava is monitored, this vessel will contain a number of gas bubbles before any are noted in the arterial system. In some cases (e.g., when viewing a small field through a microscope), researchers have seen bubbles moving prodromically in an arterial branch when the conjugate venuel is bubble-free. The arterial phase did arise from pulmonary arterialization, and an "arterial paradox" does not exist. Arterial gas tensions are thought to follow closely inspired pressures, not to be supersaturated and not to produce bubbles. This lack of nucleation was found to be true in sheep decompressed at the rate of 10 feet of sea water (fsw)/sec (Powell and Spencer, 1982). When Doppler probes were placed around the femoral artery, no gas bubbles were detected although the supersaturations (from the transit time of blood from lung to leg) were estimated to be 5 atmospheres absolute (ATA) at the surface.

During 86 decompressions in which Doppler-monitored sheep displayed Spencer Grade III or higher, bubbles were detected in the carotid artery in 7% of the subjects displaying Grade IV precordial bubbles and in 50% of the subjects with Grade IV+ [76]. Because Grade IV effects the greatest increase in RVSP, we suspect venous bubbles were arterialized in part by forced passage through A-V shunts or by the alveolar capillaries themselves. While Grade IV is not commonly encountered in human divers, it is not as rare an event as might be imagined, especially in hypobaric decompressions or in caisson workers. From the Spencer and Powell studies, it seems that the appearance of Doppler-detectable gas bubbles in the systemic arterial circulation is a rare, but not totally improbable, event. It even occurs in the absence of massive pulmonary vasculature overload (Powell and Spencer, 1980).

Arterialization occurred at definite pressures for Butler and Katz (1988) in dogs, and the mechanism would appear to be straightforward. A rise in RVSP would drive the gas phase through the pulmonary vasculature as seen in one rat study (Powell and Spencer, 1980). When other measurements were made with rats as subjects, however, the results were inconclusive. Numerous combinations of RVSP and time of appearance of arterial bubbles were seen. Similar results have also been found in pigs (Vik et al., 1989).

Cardiac septal defects must be a source of arterial bubbles, although these might be "silent" in most cases. Wilmshurst et al. (1990) found no relationship between Type II DCS and the presence of septal defects (3/34 = 24%). Curiously, these defects occur in about 25% of the general population (26/105 = 25%). Just as curious, Brubakk and Grip (1981) report finding asymptomatic arterial bubbles by Doppler devices in ascents from deep-sea diving.

Moon et al. (1991) report on 90 recreational divers who had suffered DCS (59/90 had neurologic involvement). Echocardiography on these individuals demonstrated that a "resting PFO" (i.e., a Valsalva maneuver was not necessary to provoke the passage of detectable saline contrast bubbles into the left heart) was found in 37% of the recreation divers compared to 10.9% of the controls. The odds ratio was a 4.9-fold risk for neurologic DCS when compared to the controls. Moon et al. suggest that Valsalva-induced shunts were probably not a factor in the natural history of neurologic DCS. What could not be determined in the studies of Moon et al. is the precordial Doppler bubble Grade that occurred during the dive and that resulted in DCS. This, of course,

is significant if arterialization of bubbles is to occur at all.

In altitude decompressions, gas loads to the right heart are experimentally found to be greater than in most diving decompressions. They thus pose a larger threat and increase the risk of neurologic DCS. A study reported by Clark and Hayes (1991) examines the prevalence of PFOs in those individuals who encounter Type II DCS during hypobaric training flights. They found 16% (4/24) had a patency demonstrated by saline contrast echocardiography following a Valsalva maneuver. There were no patencies with only spontaneous breathing. Clark and Hayes also found that controls demonstrated a 5% (9/176) incidence with spontaneous breathing and another 6% (10/176) with Valsalva provocation. They considered the difference to be not statistically significant. It certainly would not explain the origin of the CNS problems in the remaining 84% of the test subjects. Surprisingly, the latencies for symptoms averaged 16 hours (a range of 2 to 21 hours).

This question on the origin of CNS problems has been of importance to clinicians with regard to the mechanism of "paradoxical stroke" and its suspected embolic origin. Teague and Sharma (1991) found an incidence of right-to-left shunting of 26% at rest, and an additional 15% incidence with Valsalva strain with 2-dimensional echocardiography in stroke patients who were being evaluated for atrial septal defects (ASDs). Here, saline contrast echocardiography has been employed to identify those individuals with ASDs, including PFOs. With the addition of the TCD, a 41% incidence was detected in both groups. Lin et al. (1992) compared transthoracic versus transesophageal echocardiography, each without saline contrast, and they report that both methods possessed an ~90% success rate for ASD. Chimowitz et al. (1991) studied a few individuals with TCD (N = 4)—one of whom displayed evidence of numerous microbubbles—by an increase in the amplitude of the Doppler audio FFT spectrum; classical single bubble echoes appeared 30 to 60 sec later. However, ASDs cannot be found in all paradoxical stroke patients.

We have not yet been able to identify why one individual who had positive echoes in the left atrium by saline contrast (in the recumbent position) did not also evince bubbles (when lying likewise in the recumbent position) while displaying Grade IV bubbles during lower extremity movements. This individual was checked in the left ventricular outflow tract and in the MCA. As with paradoxical stroke, the presence of right-to-left shunts does not explain the entire problem.

B. CNS Consequences

In general, the involvement of the CNS in DCS was considered low. Less than 10% of individuals presenting DCS symptoms in the U.S. Navy were classified as having CNS or Type II DCS. However, there is a high incidence of subtle, subjective complaints in deep sea-divers with DCS such as lethargy, confusion, mental cloudiness, and a general perception that all is not well that may indicate cerebral involvement. Many of these symptoms have also been experienced by individuals who have undergone a safe decompression and who have not experienced what classically would be called frank DCS.

Vaernes, Klove and Ellertsen (1989) noted mild-to-moderate (>10% impairment) neuropsychological changes in measures of tremor, spatial memory, vigilance, and automatic reactivity in divers who had undergone saturation decompression. In many cases, these subtle effects of decompression were found to be refractory to recompression treatment (Curley et al., 1989). This has led to an increased concern for long-term, decompression-induced lesions of the CNS among the diving population (1989).

By using an injection of $^{99}Tc^{m}$-hexamethylpropyleneamine oxime and single positron emission tomography, Adkinson et al.

(1989) found perfusion deficits in the cerebral circulation of all deep-sea divers 1 month after an episode of CNS DCS. This was true even when clinical involvement of the brain was absent and only signs of spinal cord lesions were evident. This indicated that at least Type II DCS was a diffuse, multifocal disorder. Neuropsychological testing has been used to quantify some lesions (Becker, 1984; Kelly and Peters, 1975; Levin, 1975; Peters et al., 1977).

Studies by Gorman et al. (1986; 1987) have shown that gas bubbles in the cerebral arterial circulation could be expected to traverse these capillaries under certain conditions. Cerebral gas distribution is dependent upon the perfusion pressure, and this pressure in turn is an interaction of arterial blood pressure, cerebrovascular resistance, and intracranial pressure. The relation is complex since resistance is a function of blood pressure because the system maintains a relatively constant flow over a range of blood pressures (cerebral auto-regulation).

In cerebral gas infusion studies, discrete microbubbles were not seen after the gas entered the arteriolar circulation. Coalescence, or fusion, occurred and cylinders of gas formed. Entrapment occurred in vessels when the diameter was reduced to 50 to 200 micra. Transcapillary passage was dependent on systemic blood pressure and embolus length, L. If the embolus length in this vessel was >5000 micra, blockade was inevitable. If L was < 500 micra, blockage never occurred. Intermediate gas bolus lengths (500 < L < 5000 micra) were found to pass within 3 minutes. These values accord with those of Masurel et al. (1989), who calculated that a bolus would become trapped when its length exceeds 10 times its radius.

It is possible to make some estimates from these results. If the volume V of a cylindrical capillary of length L and radius r is given by

$$V = \pi r^2 L$$

calculation shows the following:

$$V_{500\mu} = 7.7 \times 10^6 \text{ [microns}^3\text{]}$$

$$V_{5,000\mu} = 77 \times 10^6 \text{ [microns}^3\text{]}$$

With the lower boundary of detectable gas bubble radii as r = 50 micra, the volume V of such a bubble can be calculated from $V = (4/3)\pi r^3$ as 3×10^5 cubic microns. We could determine the number of such gas bubbles needed to fill the 5000 micron-long capillary and determine that approximately 260 gas bubbles are needed. Employing Spencer's (1990) observation that one subject who sustained a postsurgical stroke demonstrated gas emboli in the MCA for 14 sec, this would arithmetically equate to 18 bubbles/sec. This would be an easily detected amount and is more than was found in severe decompressions in sheep studies (Powell and Spencer, 1980).

In situations where a Doppler probe was placed over the sagittal sinus, gas bubbles that were surgically implanted in sheep were heard just moments following their appearance in the carotid artery (Powell and Spencer, 1980). This would indicate that, in many cases, gas bubbles easily pass through the capillary circulation of the brain (as is true of other tissues as well) since a gas bubble is so highly deformable. The question of either the clinical appearance of DCS or the "silent" nature of DCS with this gas phase may rest with systemic arterial blood pressure and its ability to force cylindrical gas emboli through the brain capillaries. Among others, systolic arterial pressure will be a function of the gas load in the right ventricle and its ability to influence cardiac output. (Unfortunately, formed emboli do not possess the same property of deformability.)

The transcranial Doppler device (Aaslid, 1986; Aaslid and Lindgaard, 1986; Aaslid et al., 1982; Fujioka et al., 1989) is providing information on this question of the

presence of arterial bubbles. More data will be forthcoming in the near future.

Some evidence of the "silent" nature of some arterial gas bubbles comes from the observations that Spencer (1990) made with the transcranial Doppler flowmeter at surgery. When the arterial wall was invaded during carotid endarterectomy, bubble signals could be found in 38% (35/91) of the patients. Spencer notes,

> "It is clear that not all of the detected emboli signals produced symptoms. Even when many bubble signals occurred, stroke was rare. Also, since visual deficits were never noted postoperatively, even when bubbles emboli obviously had passed through the ophthalmic artery, the retina must be relatively unaffected by them."

However, the lessons from these observations in anesthetized individuals must be applied cautiously to nonanesthetized subjects because of the profound changes in cerebral metabolism and autoregulation that occur during anesthesia.

Recent findings of (Hills and James, 1991; Hills, 1992) concerning the hydrophobicity of the endothelial lining of brain tissue capillaries and possible damage by gas bubbles residing within them give us reason to be concerned about damage even in the absence of a temporary focal hypoxia. The significance of the findings, or even their veracity, is not yet known.

C. *Appearance of CNS Symptoms as the TR Increases, the Concept of a Threshold*

In studies where rats were decompressed from pressure, measurements of the RVSP indicated that arterialization did not always occur at specific elevated pulmonary artery pressures (fig. 3-5(a-e)). These findings might be specific to the experimental preparation (rat), but they did indicate that the pressure for bubble "breakthrough" varied following decompressions. The pressure for breakthrough appears to be more regular with an anesthetized dog and an air bubble infusion, but the "breakthrough" pressure is above that seen following decompression (*vide infra*).

In sheep and rats injected with air by means of an indwelling venous catheter, a relationship exists between the appearance of gas bubbles in the arterial circulation and the elevation of RVSP by gas bubbles in the pulmonary microcirculation. A quantitative but invasive system method, which is limited to animal subjects, determines the volume V of the inert gas [present as bubbles] reaching the pulmonary vasculature and measures the increase in right ventricular systolic pressure P_{RVSP} (Powell and Johanson, 1978). This increase follows the equation

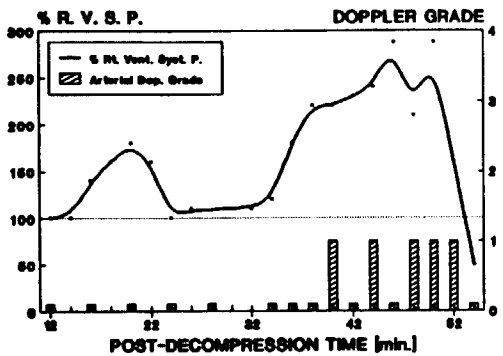
$$P_{RVSP} = 100.7 - 406V + 1.056(10^5)V^2 - 2.4(10^6)V^3 + 2.13(10^7)V^4 - 6.7(10^7)V^5$$

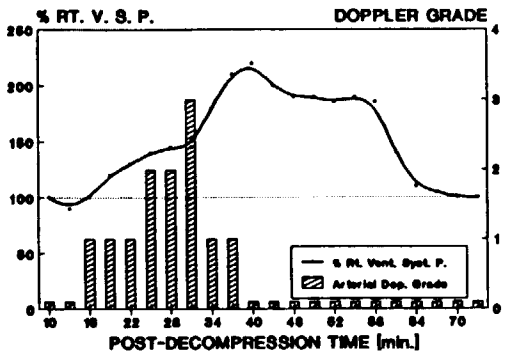
with $r^2 = 0.981$.

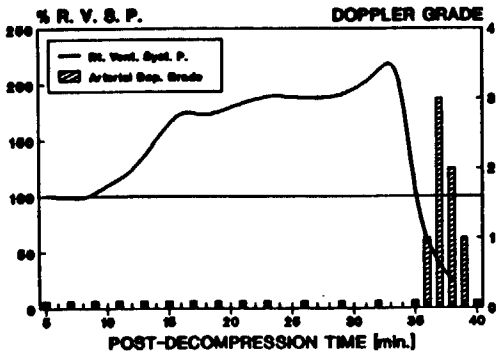
In figure 3-6a, we note that "breakthrough" does not occur until the pressure is on the order of 160% of preinjection control. This represents the injection of considerable volumes of air. When the same subjects are dived (on air), the rise in RVSP is considerably smaller (fig. 3-6(b)). "Breakthrough" still occurs, however, but with apparently smaller gas bubble loads. This is possibly the result of bubbles of considerably smaller radius forming.

The appearance of neurologic or respiratory DCS in rats (Powell, 1971) does not occur until a certain gas bubble load appears in the circulatory system. Figure 3-6(c) indicates that, as inert gas loads increase (through a lengthening of bottom time), the type of DCS observed changes from joint problems to CNS or to respiratory DCS. This indicates a threshold effect in which a certain minimal amount of free gas is required for a biological effect.

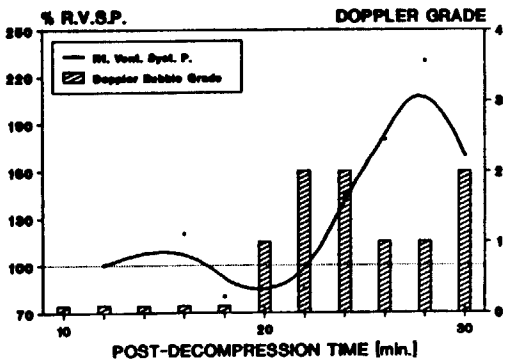
- BUBBLES DETECTED IN THE AORTA OF A RAT WHILE GAS WAS INFUSED.
- THE RIGHT VENTRICULAR SYSTOLIC PRESSURE (RVSP) WAS MONITORED.
- THERE IS NO GOOD CORRELATION IN THIS MODEL BETWEEN RVSP AND "ARTERIALIZATION." CORRELATION IS BETTER WITH A DOG MODEL.



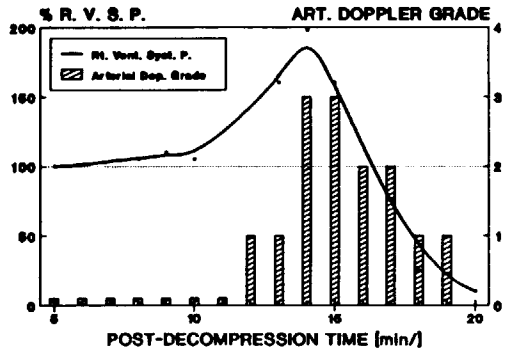




(c)

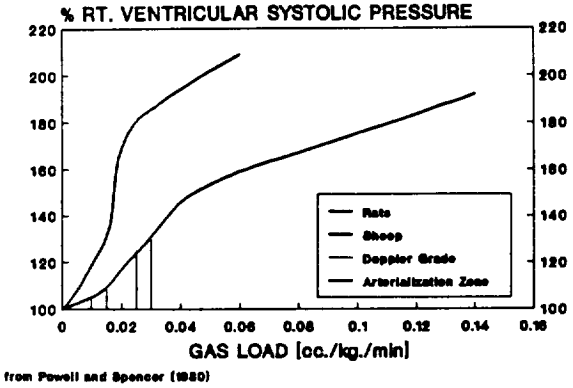


(d)

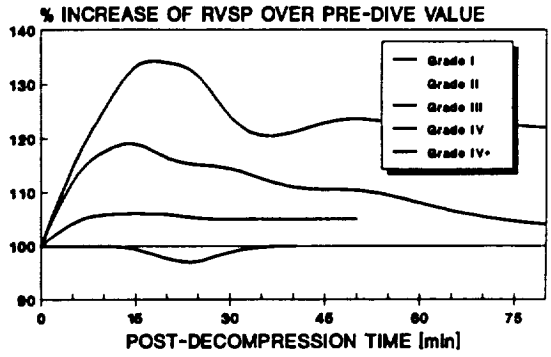


(e)

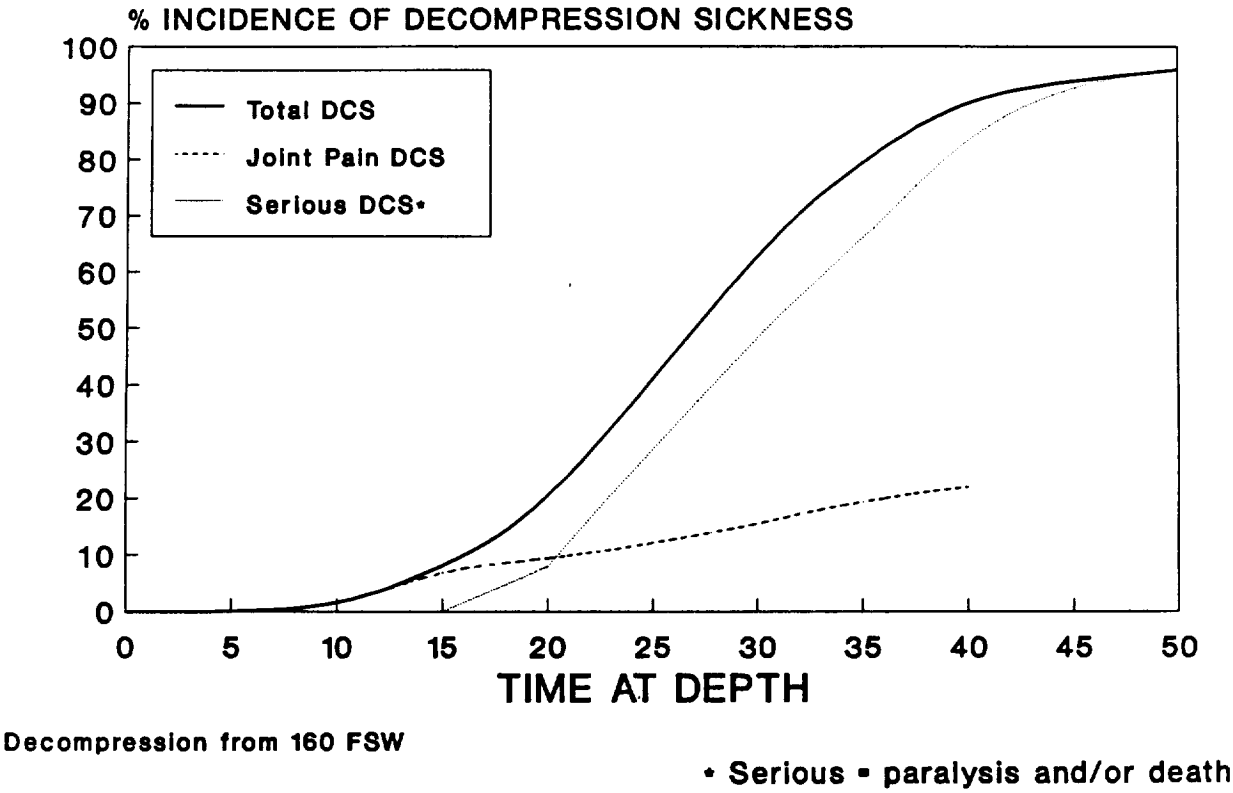
Figure 3-5. Arterial gas bubbles.



(a) RVSP versus injected gas loads.



(b) Elevation of RVSP with differing gas loads.



(c) DCS in rats.

Figure 3-6. Breakthrough occurrence.

D. Threshold Levels for Severe DCS Occurrence

An analysis and fit to a Hill equation by Conkin et al. (1987) for severe DCS—that is, a problem requiring recompression to site level [test termination] or a reoccurrence of DCS after the test—yields

$$DCS_{severe} = [(TR - 0.78)^{2.5} / (TR - 0.78)^{2.50} + 17.61)]$$

From this we can calculate the expected incidence of severe DCS for any decompression.

Let us examine the expectation for a decompression to the cabin altitude of a commercial airliner. Limiting this conservatively to 6500 feet, the cabin pressure is 11.56 psi and the $TR_{360\ min}$ would be approximately 1.005. This would yield an expectation value of 0.00137 for severe DCS. If on the order of 10,000 commercial fights per day are made throughout the world, we might expect 14 case of severe DCS per flight. This would need to be multiplied by the average passenger load. Clearly no such incidence is ever observed, however, and it indicates that the function is bounded at a value above TR = 1. In the 568 man decompressions reported and analyzed by Conkin et al. (1987), there are ***no*** indications of ***severe*** DCS below TR = 1.4.

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APPENDIX

I. Biophysical Aspects of Gas Transport and Gas Phase Formation

A. Basic Processes

Inert gas exchange occurs between the blood in the capillaries and the tissue through which it passes. The dissolved gas is at partial pressure p and the starting pressure is p_o. The difference is $\Pi = p - p_o$. The generalized equation for gas transfer is

$$\partial\Pi/\partial t = -\lambda\Pi$$

If diffusion and perfusion are included, the generalized Fick-Fourier equation applies

$$\Psi\,(D\bar{V})\,\partial\Pi = \partial\Pi/\partial t + \kappa\Pi$$

where κ is a perfusion time constant. Solutions depend on the initial and boundry conditions but can always be put into the general form

$$p - p_o = (p_i - p_o)F$$

where κ is the residue function and contains time and position information. For ***perfusion limited*** systems, the transport equations are of the type

$$\partial p/\partial t = -\lambda\,(p - p_0).$$

For the ***diffusion limited*** case, the describing equation is

$$D\,(\partial^2 p/\partial x^2) = \partial p/\partial t$$

the solution of which is dependent on the boundry conditions. In the case of altitude decompression, the tissues all start at saturation and the transport equations describe dissolved gas elimination. Since tissue nuclei ("seeds") are present, however, much of the dissolved gas is shunted into these "sinks" and the problem is rendered more difficult because it is a two-phase system. We are generally more concerned with *in vivo* bubble production processes.

The production of a gas bubble in a liquid is a process that first requires the creation of a void or cavity in the fluid, a process known as *"cavitation."* Water is unique in its high cohesive energy that exists as a consequence of its hydrogen-bonded structure. These bonds not only result in a relatively high boiling point for a liquid of water's molecular weight but also in the difficulty in fracturing the fluid and creating the cavity that, during decompression, quickly fills with the dissolved inert gas.

To fracture pure water, the theoretical limit requires the gas supersaturation be on the order of 200 to 4000 atmospheres [atm.]. The generation of a separated gas phase from a supersaturated solution involves a large entropy change and is referred to as *"suppressed transformation."* Examples include the superheating and supercooling of water, the formation of fog droplets, and the supersaturated solutions of solids in a liquid. Phase transformations proceed more easily when "assisted." This is often accomplished in real physical systems by the presence of either impurities or mechanical forces.

Some form of "stress assisted," or mechanical, mechanism is postulated to be responsible for the genesis of a decompression gas phase in tissue. Theoretical treatments to describe this have been deficient, and recourse has been taken to experiment to obtain the requisite parameters. Depending on solubility, it was found that a supersaturation of several hundred atmospheres is required in pure water (fig. A-1), and it has been known for one and a half centuries that a change of two atmospheres of pressure is the maximum attainable in humans (i.e., "impure" water).

Once a spherical bubble has been formed, the conditions for stability are given by the Laplace equation

$$\Delta P = P_{gas} - P_{ambient} = 2\gamma/R,$$

where P_{gas} is the pressure of the gas within the bubble, γ is the surface tension of the fluid medium, and R is the radius of the bubble. Because of the large effect of surface tension, the internal pressure of a gas bubble of R = 0.01 micron at 25°C is 143 atmospheres. Smaller, nascent bubbles would have considerably higher internal pressures.

Using a kinetic approach, Becker and Döring viewed a process of creation of a cavity by random fluctuations in molecular positions of water molecules. The rate of bubble production was Q and required a critical energy E_c described by a Boltzmann distribution

$$Q = Z\, e^{(-Ec/kT)}.$$

Weathersby et al. (1982), as did others, proposes that the energy of bubble formation Ec is given by

$$E_c = 4\gamma\pi r^2 + (4/3)\pi r^3 P_B[\ln(P_B/P_o)]$$

for a spherical bubble of radius r in a medium whose surface tension is γ and with a gas pressure of P_B within the bubble and one of P in the fluid. On the basis of activation energy kinetics, Weathersby et al. did not predict sufficient probability of bubbles unless the partial pressure considerably exceeded ambient pressure and the surface tension was small.

Work must be done on a microvolume of the system before a gas bubble of critical radius R can be formed. Aspects of this problem led to the creation of the first superheated liquid bubble chamber by Glaser in May 1952. In Glaser's analysis, a phase change in the superheated liquid (diethyl ether) was effected by the deposition of similarly charged ions from the impinging radiation. [It was later determined that the phase change occurred because the radiation produced localized heat spikes.] In decompression, kinetic activity is postulated to assist in cavity formation. In the hypothesis of this paper, the suggestions of E. N. Harvey are used wherein preformed nuclei reside in the tissue for short periods of time.

1. Nonspontaneous Nucleation

Small volumes of a gas phase (*"micronuclei"*), or "seed" micronuclei, may exist in hydrophobic crevices exposed to the aqueous environment. It is commonly observed *in vitro* (in instances not involving decompression) that gas bubbles do arise from micropores in hydrophobic materials previously exposed to air. These surfaces lose their ability to promote bubble formation when subjected to hydrostatic pressure since, it is surmised, their nuclei collapse. It has been shown by calculation that, in acutely angled hydrophobic crevices, a gas phase may spontaneously arise by statistical fluctuations in the thermal motion of the dissolved gases (Ward et al., 1983; Tikuisis, 1986). The location in cells of such regions of hydrophobicity directly exposed to the aqueous environment is unknown.

Micronuclei may exist prior to decompression and may be created by mechanisms described below. These nuclei would have lifetimes probably on the order of hours (and possibly a day). The most telling evidence that we have concerning the presence of these tiny gas volumes is the production of visible gas bubbles by the mechanism of *isobaric gas countertransport* (Lambertsen and Idacula, 1975). These nuclei are probably generated by "spontaneous" nucleation mechanisms.

2. Spontaneous Nucleation

"Spontaneous" refers to the ability of a gas phase to form without the prior

condition of the presence of a stable gas micronucleus. It is necessary that sufficient energy be deposited in a small volume within the liquid such that phase separation can result. In living (i.e., moving) systems, these energy density fluctuations are the result of kinetic activity. Under this heading, we grouped "homogeneous" and "heterogeneous" nucleation.

(a) *Homogeneous nucleation*

This process involves the rupture of the water structure to create a cavity; surfaces containing gas are not involved. As mentioned previously, cavitation effected solely by supersaturated gas in still (non stirred) water does not occur readily (Hemmingsen, 1975; 1977). *Negative hydrostatic forces* capable of rupturing the water structure (overcoming its tensile strength) in an environment free of nuclei can be created by mechanical forces. For example, fracturing can occur when liquids pass through a constriction, which is termed Reynold's cavitation (Dean, 1944). The microcavitation hypothesis of Hennessy (1989) wherein microbubbles are created by the motion of heart valves might explain the differences between bed-rested and ambulatory subjects, but the theory does not explain the differences between kinetically active and inactive tissue.

Nucleation that results from *shock waves* is the product of a rupture of the water structure induced by tensile forces of the compression and rarefaction. These shock waves might be produced in the lower appendages when walking. *Tribonucleation* (Hayward, 1967) can effect the formation of a gas phase when two surfaces are brought into contact with one another and then separated. In a process described by Banks and Mill (1953, and termed "tacky adhesion") and Campbell (1968, and termed *"viscous adhesion"*), negative forces (tensions capable of overcoming the tensile strength of water) are generated when adjoining surfaces are separated. The forces experienced during withdrawal can be considerable.

If two circular plates of equal radii r are separated, the negative tension at the center of the disks is given by

$$P_{tension} = 3\eta v\ r^2 / l^3,$$

The theoretical negative tension $P_{tension}$ in the liquid of viscosity η [dynes-sec/cm^2], with v the velocity of separation [cm/s], r the radius of the disks, and l the separating distance. For example, when v = 0.1 cm/s, r = 0.1 cm, and l = 10^{-4} cm, then $P_{tension}$ = 29.6 atm.

It is proposed here that this adhesion mechanism **generates gas micronuclei in capillaries when the walls collapse together with muscle activity and then are quickly separated,** leaving the nascent nucleus filled with water vapor, oxygen, inert gas, and carbon dioxide. These micronuclei, which will quickly adsorb surface active molecules, have short but finite lifetimes (up to approximately 10 hours), may reside in crevices between capillary endothelial wall and could be assisted in their genesis by "moderately hydrophobic" capillary endothelium (Hills, 1989). Thus, Doppler-detectable gas bubbles are primarily from muscle tissue, and their number have also been reported by Pimlott and Cross (1990) to correlate with plasma myoglobin titers.

(b) *Heterogeneous nucleation*

This is produced by the adsorption of gas on to hydrophobic particles, and the surface *per se* is the important characteristic, not the shape; e.g., a cavity. It acts as an accumulator to bring a sufficient number of gas molecules into close proximity to form the nascent nucleus. Hills (1966) and Plesset (1969) propose such hydrophobic phase boundaries as locii for the formation of a decompression gas phase. Such a boundary would be thermodynamically and kinetically favorable to reduce the energy necessary for the formation of the free gas phase. The

Boltzmann factor for the formation energy E_c would be

$$E_c = [(4/3)\pi\gamma_{lv}r^2] + [(4/3)\pi r_o^2(\gamma_{vs} - \gamma_{ls})]$$

where the terms γ_n represent the surface tensions of the liquid-vapor, vapor-solid, and liquid-solid interfaces. The formation energy represents the probability that a formation process will occur. Once a short distance from the surface, however, the advantage is lost. This is the apparent reason that "seeding" a supersaturated solution with hydrophobic "motes" meets with little success.

B. In Vivo Gas Phase Formation

1. Animal Subjects

Mechanical forces are postulated to be responsible for the relative ease with which a gas phase forms in living tissue. The vast majority of evidence for muscle and joint activity as a provocative agent for stress-assisted gas phase formation derives from animal experimentation. Early work was directed towards the genesis of a gas phase in the crews of high-altitude bombers during World War II. Harvey (1951; Harvey et al., 1944) demonstrated the presence of stable tissue gas micronuclei. Whitaker et al. (1944) and Harris et al. (1944) showed that rats (fig. A-2) and frogs (fig. A-3) that had exercised at altitude displayed a greater number of vascular bubbles than those who had rested. The exercise effected an increase in some tissue component (postulated to be either gas micronuclei or carbon dioxide), which decreased with time since exercise prior to decompression produced increased vascular bubbles in frogs; but the promotion decreased as the interval between exercise and depressurization lengthened (fig. A-4) Vigorous activity of frogs also promoted the growth of a free gas phase following decompression from hyperbaric conditions (fig. A-5). These results are likewise indicated by more contemporary studies by Evans and Walder (1969), Vann et al. (1980), and Daniels et al. (1984).

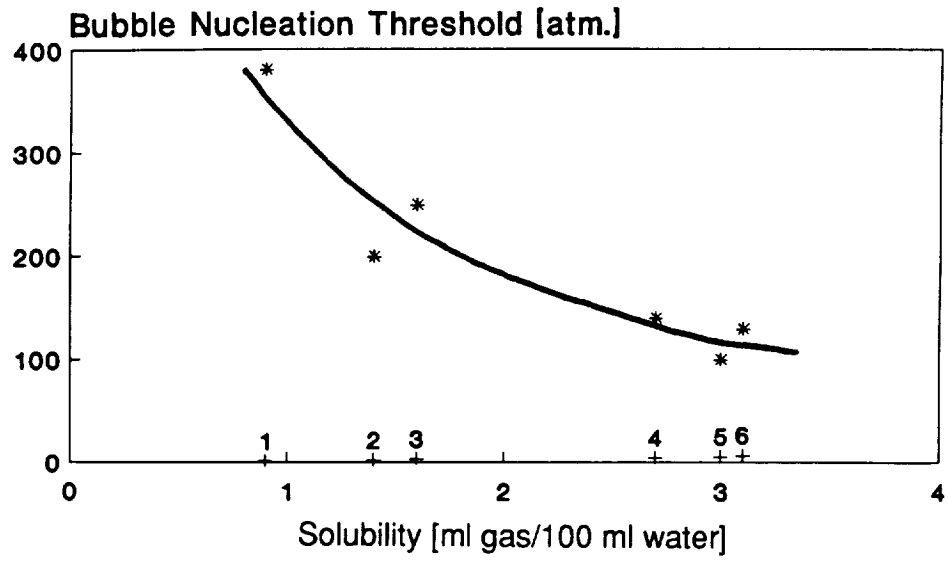
Other work by Blinks et al. (1951) and Hemmingsen (1989) indicates that stable tissue gas micronuclei are of lesser importance and are overpowered by other mechanical mechanisms under physiological conditions. These conditions are muscle and joint movement, which are described above as "viscous adhesion." Experiments using crabs as subjects demonstrated a resistance to the formation of visible decompression gas bubbles (seen through the carapace) when the feet of the crabs were stabilized with epoxy adhesive (fig. A-6). A similar decompression effected when the legs were no longer immobilized produced numerous visible gas bubbles.

Animals are known to be quite resistant to decompression sickness when anesthetized and quiescent, although the endpoint of these studies is "decompression death" (Powell, 1972 a, b); these studies employ very severe pressure reduction profiles. In a reported Russian experiment (Genin, 1949), hibernating squirrels were able to survive a very severe hypobaric decompression. Powell and Spencer (1980) found that considerably greater numbers of gas bubbles could be ultrasonically detected in veins draining kinetically active tissues (e.g., muscle) than in nonactive ones (kidney and brain).

Small animals are known to be more resistant to the effects of large pressure reductions than are humans. Classically, this has been attributed to perfusion differences. Another explanation for this would be the fact that laboratory animals are quadrupeds whose daily dynamic loading (and ambulatory activity) is distributed over four limbs. Furthermore, when in a laboratory cage, they experience greatly restricted movement from day to day ("small-cage restraint").

2. Human Subjects

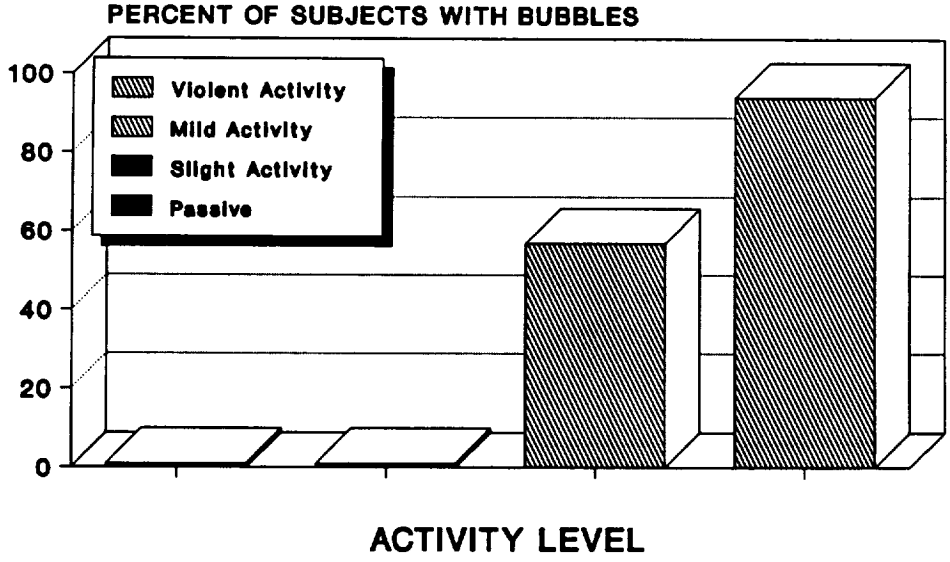
It is known that human volunteers display an increased tendency to DCS following exercise. Figure A-7, redrawn from



Redrawn from Hemmingsen, 1989.

1=helium; 2 = nitrogen; 3 = hydrogen;
4 = oxygen; 5 = methane; 6 = argon.

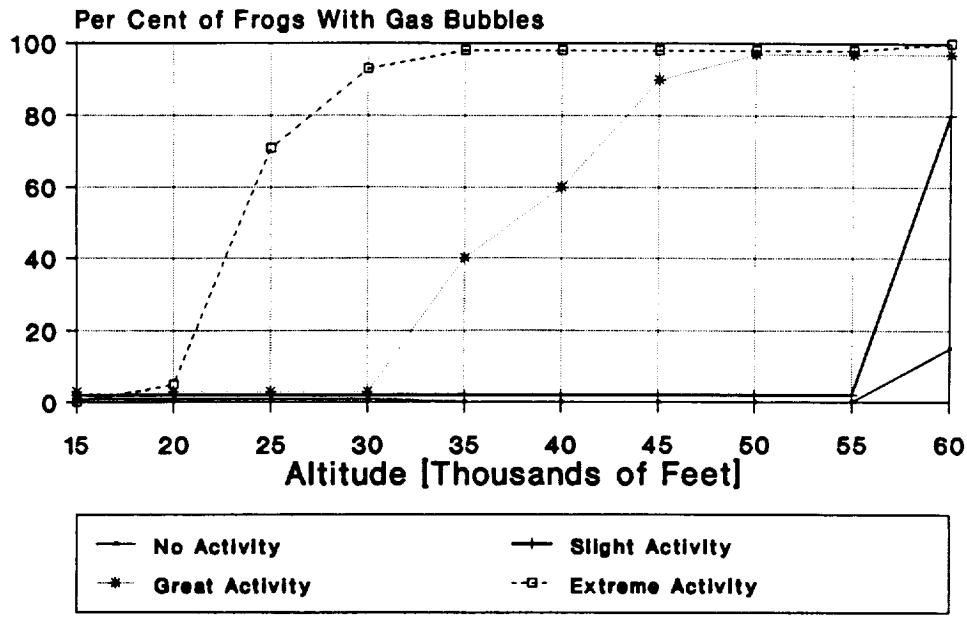
Figure A-1. Homogenous nucleation thresholds for various gases in water.



After Whitaker et al., 1944.

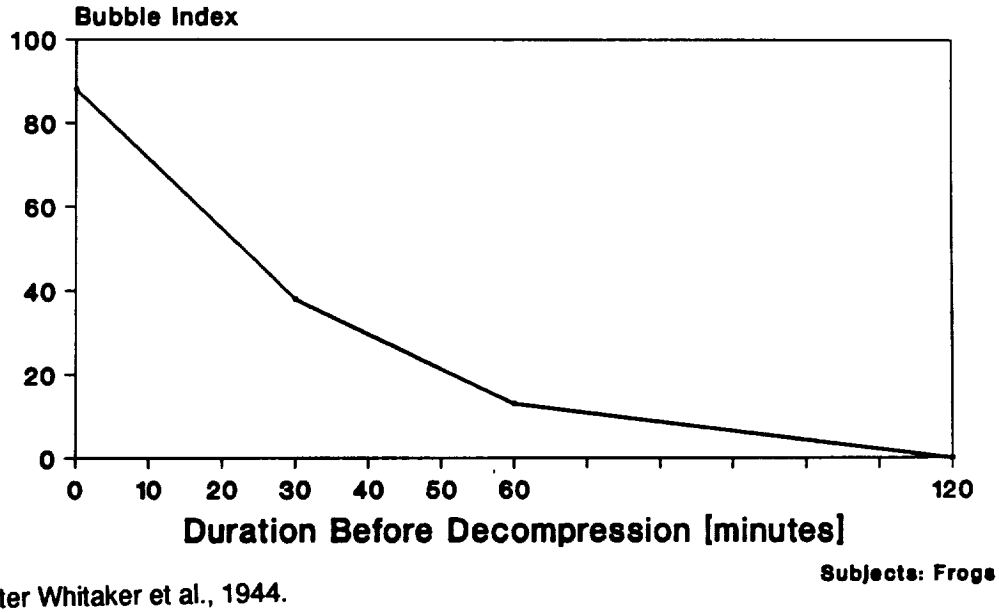
Subjects: Rats

Figure A-2. Hypobaric decompression bubble formation and level of activity.



From Whitaker et al., 1944.

Figure A-3. Decompression bubbles versus exercise in frogs.



After Whitaker et al., 1944.

Figure A-4. Gas bubble formation from exercise before decompression.

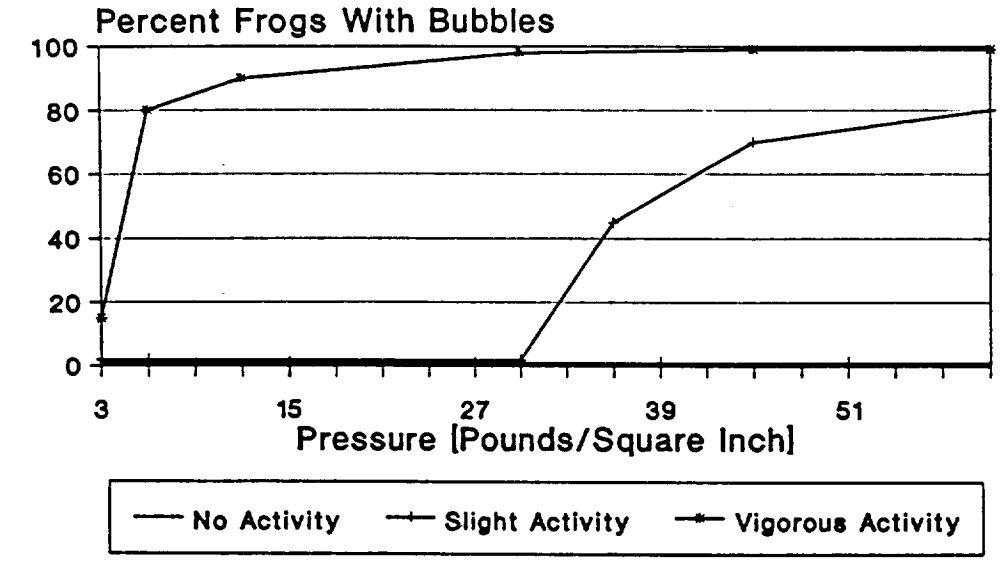
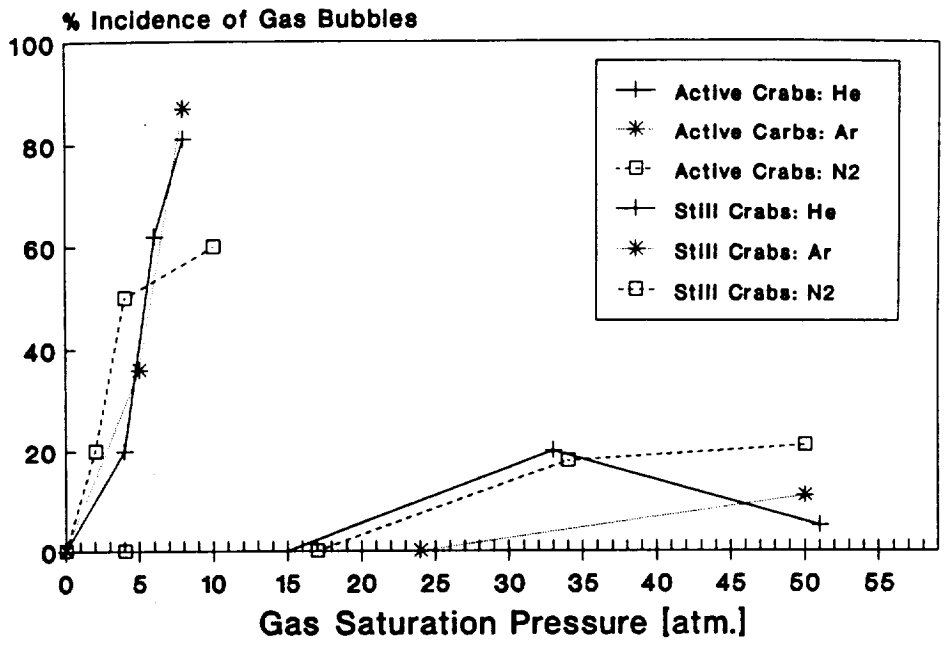
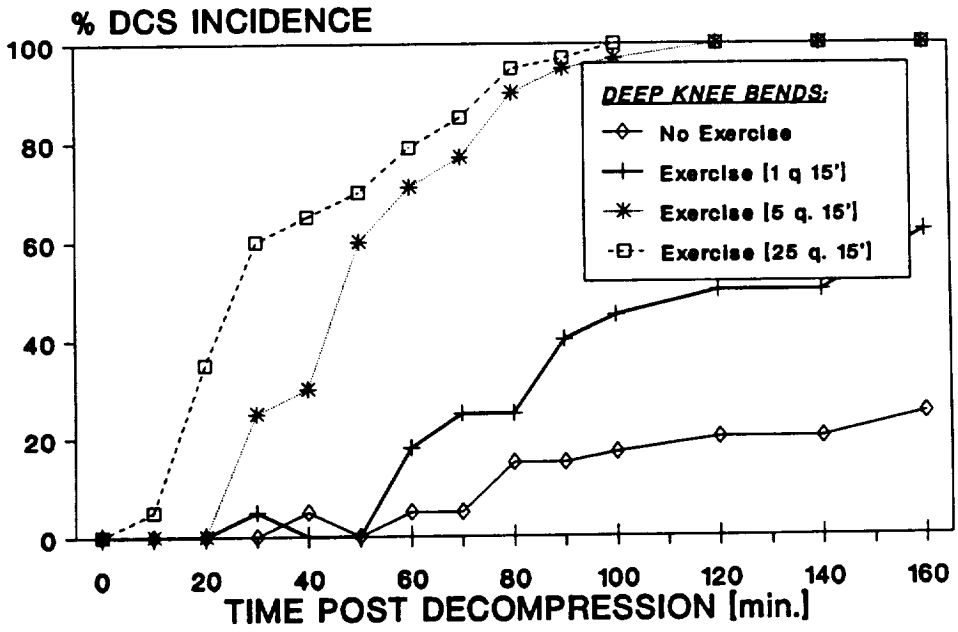


Figure A-5. Hyperbaric decompression and DCS incidence with activity following decompression.



After Hemmingsen (1989).

Figure A-6. Bubble formation in the joints of active and resting crabs.



Redrawn from Ferris and Engel (1952).

Figure A-7. Altitude DC S during graded exercise versus rest.

Ferris and Engel (1951), shows the number of men who developed DCS in their lower limbs while performing step (stair climbing) exercises at simulated altitude. Additionally, the response was proportional to the degree of exercise and there was an indication that the subjects reached a plateau where further exercise did not produce an increase in the number of responders (or in the time of response).

II. Doppler Ultrasound and Time-intensity Analysis

A. Initial Work

The first successful formulation of decompression schedules was devised by J. S. Haldane (Boycott et al., 1908). It utilizes the concepts of (1) multiple tissues and (2) exponential uptake and elimination of inert gas resulting in tissue half-times. Analysis of the concept and the testing of tables was for many years by means of "bends/no bends" endpoints. Newer diagnostic technologies, in the form of ultrasound, have arisen since the late 1960s (Spencer and Campbell, 1968; Gillis et al., 1968; Powell, 1971).

Doppler ultrasonic bubble detection techniques have been employed for approximately 2 decades to evaluated decompression procedures for deep-sea divers (Spencer, 1976). Powell (1974) introduced the concept of "probability of decompression outcome" associated with the maximum precordial Doppler grade. Later this "probability concept" was expanded to include men (Powell and Johanson, 1978); a parallel study by Nashimoto and Gotoh (1978) reached similar conclusions. Gardette (1979) extended the probability methodology to include saturation decompressions. The technique has been further expanded in recent years to include many subjects in saturation, "bounce," and altitude exposures. A compilation by Vann et al. (1982) includes more than 1000 individuals and relates their Spencer Grade (Spencer and Johanson, 1974) to the final outcome (bends/no bends) of their decompression.

B. Integral Concept

Experimental data (Powell and Spencer, 1980) show that a time-integrated Spencer Doppler grade is related to decompression stress (fig. A-8). The Doppler gas phase determined in the precordial mode from different decompression stresses [achieved through a variation in the bottom time] yielded a regular and orderly progression in both the intensity and duration realm.

In place of a simple "bubbles/no bubbles" technique of analysis using a single, maximum Spencer Doppler grade, a time/intensity method may be employed that will relate the expected probability of decompression sickness (DCS) to other decompressions performed at unit gravity. This is an algorithm to determine objectively an individual's decompression stress; it was first employed by Nishi et al. (1980) and Powell (Powell and Spencer, 1980). It consists of an integration over time of the precordially determined Spencer Doppler bubble grade. The formula first suggested by Nishi et al. (1980) was

$$D.S. = \{100/4^a\,(t_j - t_o)\} \sum_{i=1}^{j} [(t_i - t_{i-1})(d^a{}_i + d^a{}_{i-1})/2]$$

where d = Spencer bubble grade at t_i, ($d_o = 0$),
j = number of observations,
t_i = time of last observation ($t_o = 0$), and
a = a parameter to adjust for nonlinearity in the Doppler grade.

An alternative computational method, based on elevations in the right ventricular systolic pressure (RVSP) with gas embolization, was used in this study to adjust for nonlinearity in the Spencer Grades of Doppler data.

Other workers have used this integral concept in principle. A form of time-intensity analysis has been employed by Dunford and Hayward (1981) and by Eckenhoff et al. (1989) in the analysis of their diving data. Powell and Spencer (1981) used it to compare the decompression stress associated with different environments (cold/wet, warm/dry, etc.)

C. *Conversion Factors (Transfer Functions)*

To determine the gas volumes, two steps were required. The first step related the rise in RVSP to the volume of air introduced during air injection through a catheter (fig. A-9). The second step required that the rise in RVSP be measured, following decompression, while the precordial Doppler grade was measured yielding an average gas volume for a given Spencer precordial Grade. A transfer function then converts Spencer Grade into approximate volume: 0 = 0, I = 1, II = 4, III = 6, IV = 10.

Data from precordial Doppler ultrasound monitoring are currently depicted in a form that relates a given sound pattern to a number referred to as the "grade" (Spencer and Johanson 1974). The "grade" is, however, only a relative scale and is not necessarily directly proportional to a given quantity of intravascular gas. One method to convert from "Spencer Grade" to a gas volume uses the quantitative measurements of Powell and Spencer (1980) that related the volume of the gas phase present in the pulmonary artery with the Doppler grade, both being simultaneously measured.

A measure of "decompression stress" can thus be formed from the average Doppler "gas volume" versus time for all of the subjects exposed to a decompression (given tissue ratio (TR)) (fig. A-10). This TR is the ratio of inert gas (nitrogen) in a tissue (taken in these cases to be the 360-minute half-time tissue; Conkin et al., 1987) to the ambient (hypobaric chamber) pressure.

D. *Generation of Doppler-Detectable Gas Bubbles*

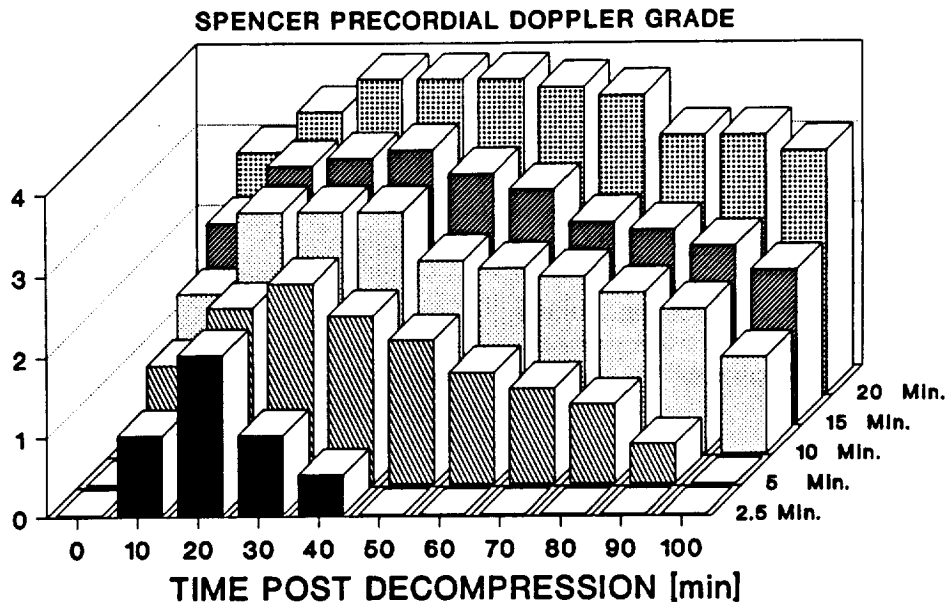
Banks and Mill (1953) described a process for the generation of low-pressure regions ("tacky adhesion") along with Campbell (1968, who termed it *"viscous adhesion"*). In this mechanism, negative forces (tensions capable of overcoming the tensile strength of water) are generated when adjoining surfaces are separated; the forces during withdrawal can be considerable. If two circular plates of equal radii r are separated, the negative tension at the center of the disks is given by

$$P_{tension} = 3\eta v\ r^2 / l^3,$$

The theoretical negative tension $P_{tension}$ in the liquid of viscosity η [dynes-sec/cm^2] is given, with v the velocity of separation [cm/s], r the radius of the disks, and l the separating distance. For example, when v = 0.1 cm/s, r = 0.1 cm, and $l = 10^{-4}$ cm, $P_{tension}$ = 29.6 atm.

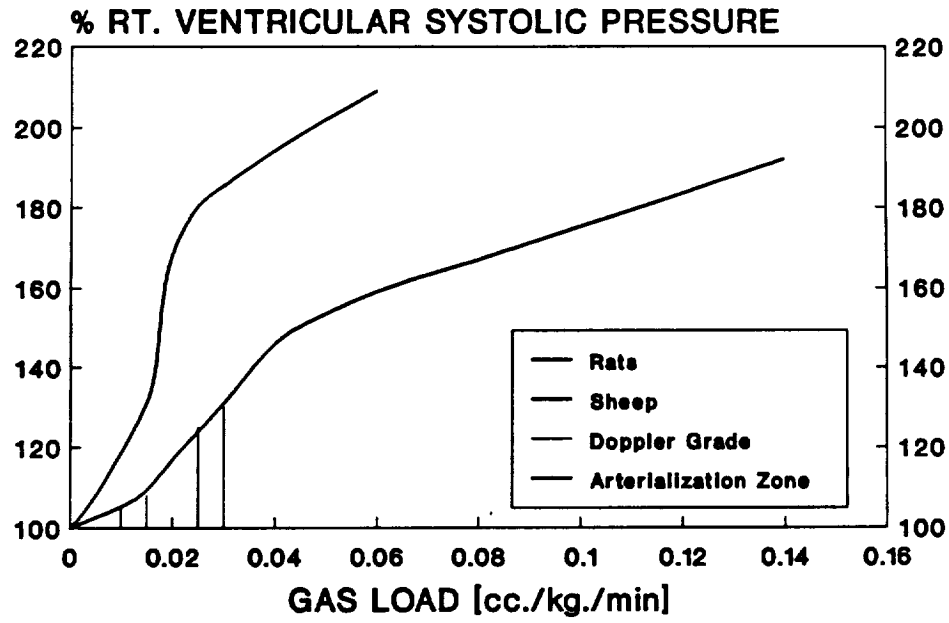
Such a system would be capable of generating the gas bubbles detected emanating from capillaries by the following sequence of events:

- First, **contraction of muscles** would also **squeeze the flexible capillary** walls together.
- Second, the vessels would **rapidly expand with an extension movement** that changes the dimensions of the muscle.
- Third, the **vessel endothelium** would be **approximated** and then rapidly separated, creating a reduced pressure area. The inward flux of gas (oxygen and carbon dioxide) and vapor would produce a cavity stabilized for a short period of time.



From Powell and Spencer (1980).
Subjects: Sheep

Figure A-8. Spencer Doppler Grades in air dives to 160 fsw for differing bottom times.



From Powell and Spencer (1980).

Figure A-9. RVSP versus injected gas loads.

- Fourth, this cavity world grow by the inward flux of gas with decompression oversaturation.

Several individual physiological factors could be expected to be of importance, and these would vary from individual to individual and possibly from day to day.

1. The **flexibility of the vessel wall** which would allow it to produce a low-pressure region and micronucleus by viscous adhesion;

2. The **composition of the basement membrane** of the endothelial cell wall (e.g., degree of hydrophobicity), which might **foster the formation of a vapor/gas surface** that would rapidly fill with dissolved gases;

3. The **gas permeability** of the **endothelial walls**, which would allow dissolved inert gas to enter and stabilize the micronucleus; and

4. The **biomacromolecules (ampholytes) in the serum**, which would stabilize the micronucleus by reducing the **effective surface tension.**

Similar systems of contracting walls have been investigated as one origin of gas bubbles from the flexible tubes and roller pumps of extracorporeal circulatory systems (Hanneman and Barile, 1973). There is also biochemical evidence of the muscular microcirculatory system originating Doppler bubbles in that the number (Grade) of Doppler gas bubbles correlates with the titer of serum myoglobin (Pimlott and Cross, 1990).

III. Stable Gas Micronuclei

Stable nuclei probably cannot exist since that would imply that the organic "skin" would be impervious to the diffusion of gas and, furthermore, that such an entity could not grow by the inward diffusion of gas since the organic "skin" would be impermeable. Therefore, there must be a finite lifetime for the gas micronucleus, and this micronucleus possesses a finite permeability of flux **q** given in terms of the *permeability coefficient* **K**, the wall thickness **d**, and the pressure difference ΔP, or

$$q = K \Delta P/d$$

The coefficient **K** is further resolved into the solubility **c** and the diffusion coefficient δ, such that we have

$$q = c \delta \Delta P/d$$

The loss of gas from the nucleus would be rapid but certainly not instantaneous; it might perhaps require hours. It is not a requirement of tissue micronuclei that they be stable, only that they have a finite lifetime of perhaps hours. The long-term persistence of the nucleus is dependent upon the surface tension γ, which will increase the internal pressure (unless the contraction is arrested by some, as yet, unknown mechanism). Fox and Herzfeld (1954) estimated that the surface film of a small bubble contains 10^8 to 10^{10} organic molecules. As the bubble contracted, the surface film became compacted and slowed the contraction rendering the lifetime greater than seconds. An estimate of this can be made. Fox and Herzfeld (1954) estimated the amount of gas diffusing out from the surface of a gas bubble. If this process is very slow, it can be considered quasistatic. If the concentration of dissolved gas in a liquid at some distance from the bubble is c_∞ and the concentration is c' at the surface of a bubble of radius **a**, the concentration **c** at a distance **r** is given by

$$c = c_\infty + (c' - c_\infty)(a/r).$$

The amount of gas diffusing from the surface is given by

$$4\pi a^2 D(-\partial c/\partial r) = 4\pi D(c' - c_\infty)a.$$

If p_0 is ambient pressure and p_∞ is the equilibrium pressure (= p_0 at saturation), the number of molecules diffusing out per second is

$$4\pi Da\,(p_o - p_\infty + [2\,\sigma/a])\alpha$$

The gas content of the bubbles is measured in cc. under standard conditions

$$(4\pi a^3/3)(p_0 + [2\,\sigma/a])\,10^{-6}$$

and, therefore, the flux is given by

$$-\partial[(4\pi a^3/3)(p_0 + [2\,\sigma/a])\,10^{-6}]/\partial t =$$

$$4\pi Da\,(p_0 - p_\infty + [2\,\sigma/a])\alpha\,10^{-6}$$

If there is no undersaturation, the dissolution time t for a bubble of radius a is

$$t = (a^2/3D\alpha)(1 + [p_0 a/2\sigma]).$$

If we take the case for a gas bubble situated in a collagenous tendon (semi-aqueous tissue), we might assume the following reasonable values for nitrogen:

- α = 0.006 (Estimated for tendon; from Phelps et al., 1972.)
- D = 4×10^{-6} [cm/sec^2] (Normally given as 2×10^{-5} for water.)
- p_0 = 10^6
- σ = 20 [dynes/cm^2]

This last value is smaller than that for pure water and recognizes that the surface of the gas bubble will be modified by the adsorbate to change the *effective* surface tension.

After performing the calculations, the values in table A-I are obtained. Additionally, if we adapt values of D, which tend toward those suggested by Hills, we might use a value of $D = 2 \times 10^{-8}$—which might be realistic for tendon and which was found by Gernhardt (1991) by the method of maximum likelihood from decompression data files. (Hills employed values for D that were very small, with $D = 10^{-11}$. This would not allow growth of the gas phase by diffusion during decompression.) The results are shown in figure A-11. From this analysis, it is not unreasonable to believe that gas micronuclei could be created by tensile forces *in vivo* within tendon and ligament, and that, depending upon their initial radii, these nuclei would be stable for hours. They would be continually renewed or regenerated through musculoskeletal kinetic activity.

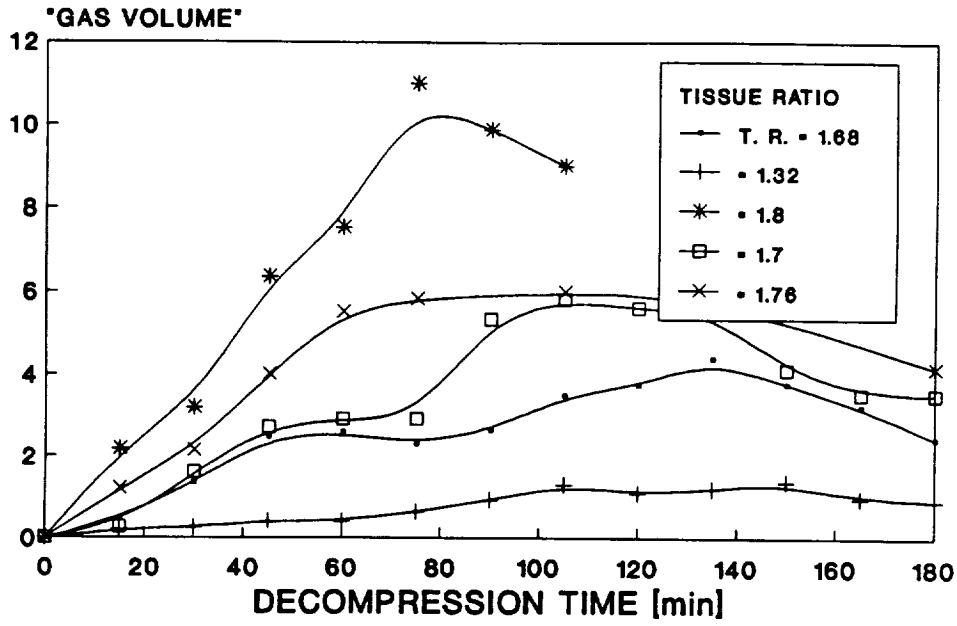
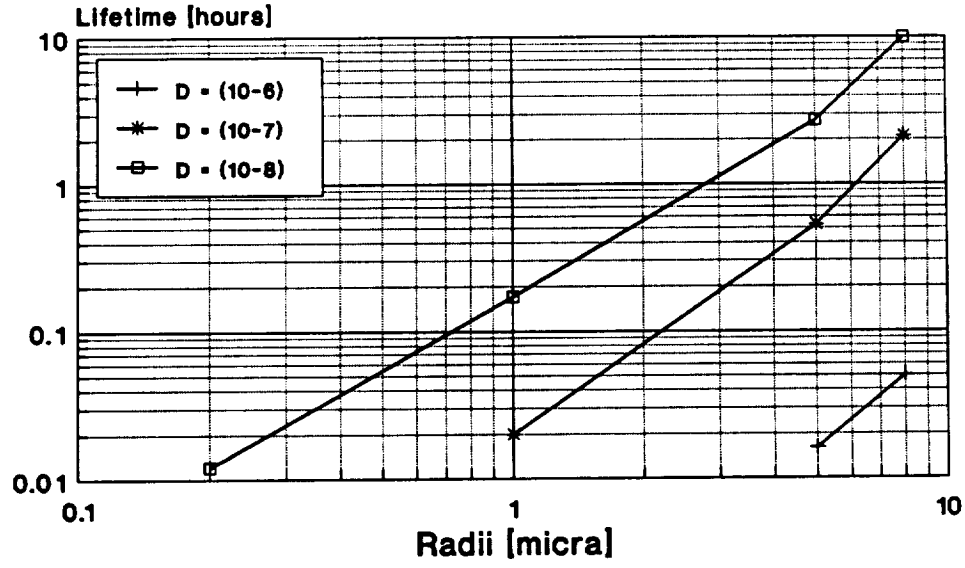


Figure A-10. Doppler "gas volumes" versus time for differing TRs.



Based on Fox and Herzfeld (1954).

Figure A-11. Lifetimes of gas micronuclei calculated with different diffusion coefficients.

Table A-I. Gas Bubble Dissolution Times

Diffusion Constant	Initial Bubble Radius	Dissolution Time
$D = 4 \times 10^{-6}$	a = 1 micron	t = 0.5 sec
	= 5 micra	t = 40 sec
	= 8 micra	t = 180 sec
$D = 1 \times 10^{-7}$	a = 1 micron	t = 70 sec
	= 5	t = 1,876 sec = 0.5 hrs
	= 8	t = 7.560 sec = 2.1 hrs
$D = 2 \times 10^{-8}$	a = 1 micron	t = 10 min
	= 5	t = 2.7 hrs
	= 8	t = 9.9 hrs

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13. ABSTRACT *(Maximum 200 words)*

The ARGO study investigated the reduced incidence of joint pain decompression sickness (DCS) encountered in microgravity as compared with an expected incidence of joint pain DCS experienced by test subjects in Earth-based laboratories (unit gravity) with similar protocols. Individuals who are decompressed from saturated conditions usually acquire joint pain DCS in the lower extremities. Our hypothesis is that the incidence of joint pain DCS can be limited by a significant reduction in the tissue gas micronuclei formed by stress-assisted nucleation. Reductions in dynamic and kinetic stresses *in vivo* are linked to hypokinetic and adynamic conditions of individuals in zero g. We employed the Doppler ultrasound bubble detection technique in simulated microgravity studies to determine quantitatively the degree of gas phase formation in the upper and lower extremities of test subjects during decompression. We found no evidence of right-to-left shunting through pulmonary vasculature. The volume of gas bubbles following decompression was examined and compared with the number following saline contrast injection. From this, we predict a reduced incidence of DCS on orbit, although the incidence of predicted mild DCS still remains larger than that encountered on orbit.

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