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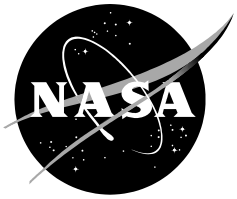

Preventing Decompression Sickness Over Three Decades of Extravehicular Activity

Johnny Conkin, Ph.D.,[1] *Human Adaptation and Countermeasures Division*[2]

[1]*Universities Space Research Association, Houston*

[2]*NASA Johnson Space Center, Houston*

June 2011

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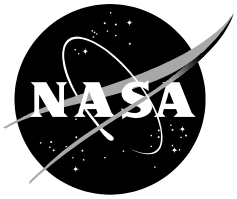

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Dedication

This publication is dedicated to the hundreds of anonymous research subjects who accepted some risk to their health to validate denitrogenation protocols for astronauts, and to those persons with the courage to work in space.

Acknowledgment

It is impossible to acknowledge by name all those involved in the testing, training, and operational implementation of 5 denitrogenation protocols used in more than 30 years of spacewalks from the shuttle, Russian *Mir* space station, and International Space Station. NASA investigators James M. Waligora, David J. Horrigan, Jr., Michael R. Powell, and Michael L. Gernhardt worked tirelessly with numerous investigators in academia, the U.S. Air Force, and international partners to test denitrogenation protocols in altitude chambers in the U.S. and Canada. Jimmy D. Adams, Andrew A. Pilmanis, and James T. Webb from Brooks Air Force Base (AFB) provided valuable consulting to NASA and conducted many NASA-funded altitude tests at Brooks AFB. Many contributed to testing at the NASA Johnson Space Center, including Vasantha K. Kumar, Philip P. Foster, Charles K. LaPinta, Charles E. Ross, Mike Fox, and Alan H. Feiveson, who provided outstanding statistical support in study design, data analysis, and consulting. Ronald Y. Nishi, Patrick J. Sullivan, and Gary W. Gray from Defense Research and Development – Toronto, along with Bruce D. Butler, Caroline Fife, Richard D. Vann, Wayne A. Gerth, Michael J. Natoli, and Neal W. Pollock safely conducted tests for NASA on the benefits of exercise to accelerated denitrogenation during prebreathe. NASA flight surgeons, including Joseph P. Dervay, were critical to bridging the gap between chamber testing and operational implementation of protocols, especially in monitoring the success of those protocols and for preparations to treat decompression sickness. Jane Krauhs and Sharon Hecht provided exceptional editing, and Tom S. Neuman was the motivation behind the report.

Disclaimer

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Abstract

The shuttle Space Transportation System has come to a close. Among the advances made during the 30-year operational life of the shuttle were those in our understanding of decompression sickness. New denitrogenation procedures were validated with research subjects in altitude chambers. Validation continued during hundreds of spacewalks that were safely performed from the shuttle, Russian *Mir* space station, and now from International Space Station. Hypobaric exposure combined with microgravity achieved through space flight afforded a unique opportunity to understand more about decompression sickness. Lessons learned included: (1) a greater understanding of the limits to depressurization to minimize evolved gas and symptoms of decompression sickness, (2) methods to accelerate denitrogenation during oxygen prebreathing, (3) insights into tissue micronuclei formation and stability, (4) differences between research and operational settings, and (5) translation of research results into effective operational prebreathe protocols appropriate for a spacesuit that operates at a pressure only 4.3 pounds per square inch, absolute, or 222 mmHg, above the vacuum of space. A spacewalk is the culmination of many hours of training under both hyperbaric and hypobaric conditions, training that must be managed to avoid decompression sickness. Flexibility in selecting both atmospheric gas composition and pressure in future exploration vehicles and habitats plus advances in spacesuit design will enable humans to exploit space without interference from decompression sickness.

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Acronyms

AFB	Air Force Base
AGE	arterial gas emboli
Ar	argon
ATA	atmosphere absolute
ATM	atmosphere pressure
CEVIS	cycle ergometer with vibration isolation and stabilization
CO_2	carbon dioxide
DCS	decompression sickness
ΔP	pressure difference
ECG	electrocardiogram
EMU	extravehicular mobility unit
EVA	extravehicular activity
FFW	feet of fresh water
FN_2	fraction of nitrogen in a bubble
FSW	feet of seawater
ISLE	In-suit Light Exercise
ISS	International Space Station
JSC	Johnson Space Center
μg	microgravity
N_2	nitrogen
NBL	Neutral Buoyancy Laboratory
NEEMO	NASA Extreme Environment Mission Operations
O_2	oxygen
P1	initial pressure
$P1N_2$	computed tissue nitrogen partial pressure
P2	final pressure
PB	prebreathe
P(DCS)	probability of decompression sickness
P(Grade IV VGE)	probability of Grade IV venous gas emboli
P_IN_2	inspired (wet) partial pressure of nitrogen
P_IO_2	inspired (wet) partial pressure of oxygen
PFO	patent foramen ovale
ppN_2	partial pressure of nitrogen
P(Serious DCS)	probability of serious decompression sickness

psia	pounds per square inch, absolute
R-value	ratio-value used by NASA, equivalent to $P1N_2/P2$
r_c	critical radius
SD	standard deviation
STPD	standard temperature [0°C], pressure (1 ATM), and dry gas
STS	Space Transportation System
TR	tissue ratio
USAF	U.S. Air Force
VGE	venous gas emboli
VO_2 peak	measured peak oxygen consumption as $ml*kg^{-1}*min^{-1}$
WWII	World War II

Introduction

The Space Transportation System (STS), in the form of the space shuttle fleet, including *Challenger* and *Columbia*, has come to a close. Historians will tell the story of the impact that this remarkable system of machines and humans has made on our nation and humanity. Among the advances made during the 30-year operational life of the shuttle were those in our understanding of decompression sickness (DCS). New denitrogenation procedures were validated with research subjects in altitude chambers. Validation continued during hundreds of spacewalks, or extravehicular activities (EVAs), safely performed from the shuttle, the *Mir* space station, and now from the International Space Station (ISS). Hypobaric exposure combined with microgravity (μ*g*) achieved through space flight afforded a unique opportunity to understand more about DCS, still a significant occupational and recreational hazard. This report explains how NASA minimized the risk of DCS in an environment conducive to evolved gas. The current NASA spacesuit operates at a pressure that is only 4.3 pounds per square inch, absolute (psia), or 222 mmHg, above the vacuum of space.[1,2]

Nature of the Problem for Astronauts

Life on Earth evolved under Earth-normal atmospheric pressure (1 ATA, 14.7 psia, 101.3 kPa, 760 mmHg) and Earth-normal gravity (1*g*). One atmosphere of pressure is 1 pressure in a range of higher and lower pressures at which we can comfortably exist. It is the rapid transition from high to low pressure, discounting isobaric inert gas counterdiffusion, that is the concern for DCS. A diver wearing a wetsuit returns to the surface after completing a task and *then* is afflicted with DCS. By contrast, an astronaut performing an EVA in a spacesuit is afflicted with DCS *while* performing a task. DCS therefore compromises the completion of the astronaut's task and, in large measure, the success of the mission. In both cases, the best plans have failed, however, and the DCS-afflicted individual seeks treatment for evolved gas. As the astronaut failed to complete an expensive task, DCS in astronauts is both a medical and a productivity concern that ultimately define acceptable risk. Acceptable risk is eventually defined, either prospectively or through trial and error.

Preventing DCS is preferred to treating DCS. Two strategies, excluding the fascinating possibility of breathing oxygenated liquid, are available to prevent DCS. The first provides a sufficient ambient gas pressure on the body by means of a mechanical structure around the body. The use of 1-atmosphere space and diver suits, counterpressure suits, submarines, and pressurized aircraft cockpits maximize human safety but are very costly in terms of engineering, complexity, materials, and inaccessibility to the environment. The second strategy exposes the body to the hyperbaric or hypobaric environment but reduces ambient pressure at a rate that avoids or limits the formation of bubbles in the tissues. The depressurization rate is made operationally relevant if partial denitrogenation is achieved before depressurization occurs. This approach takes advantage of tissue incompressibility, tissue accommodation to a quantity of dissolved inert gas, and accessibility to the environment. It is less costly in terms of engineering and materials, but is not necessarily as safe as the first approach. The second approach requires an understanding of DCS from which to develop depressurization strategies.

When a diver returns from a hyperbaric environment, or an aviator or astronaut travels to a hypobaric environment, the amount of inert gas in excess of what can be held in solution at the new, lower pressure has the potential to come out of solution to form gas spaces that can displace

or otherwise damage tissues. Displacement of tissue by trapped gas spaces or disruption of metabolic function due to embolic obstruction of blood flow can cause a wide range of signs and symptoms. The many signs and symptoms as a consequence of evolved gas and a review of treatment options for those afflicted are described elsewhere. The reader is referred to several publications* for descriptions of what aviators and astronauts need to avoid to stay healthy and productive, and treatment options if evolved gas is not prevented. One consistent observation about subjects at the NASA Johnson Space Center (JSC) is that pain-only DCS after significant denitrogenation occurs predominately in the lower body, particularly with that part of the body associated in or around the patella of the knee.[6,11] Subjects often noticed, or confirmed, a fullness, an awareness, or a frank pain when the leg was horizontally flexed with the body in a supine position. While standing or walking, this pain, fullness, or awareness would abate only to return when the leg was once again horizontally flexed.

A fundamental axiom about DCS is that a transient gas supersaturation, also called over-pressure or pressure difference (ΔP), exists in a tissue region; the sum of all gas partial pressures in that region is greater than the ambient pressure opposing the release of the gas. Expressed as an equation, supersaturation exists when ΔP is positive:

$$\Delta P = \left(\sum_{i=1}^{n} P_i - P2\right) \quad (1)$$

where P_i = the dissolved gas tension of the i^{th} gas of n species in the tissue and P2 = the ambient pressure after depressurization. The potential for bubble nucleation and rate of bubble growth are a function of supersaturation.

While gas supersaturation in the tissue is not in itself harmful, it is a thermodynamically unstable condition between the tissue and the surrounding environment. The difference between tissue gas partial pressure and ambient pressure is easily resolved with a phase transition, and some of the excess mass (moles) of gas in the form of bubbles may be accommodated by the tissue and cause no symptoms. However, when a gas space is formed due to partial or complete desaturation of a supersaturated tissue, there is a probability of DCS (P[DCS]).[12] A necessary but insufficient condition for DCS is the formation of a gas phase in the tissue. The assumption that due to evolved gas, pain results from the deformation of tissue past a critical point may not account for symptoms other than pain-only DCS, but evolved gas is certainly the primary insult for all subsequent signs and symptoms. It is not the presence or even the volume of evolved gas in the tissue that is important in pain-only DCS; it is the pressure difference between the gas space and the tissue that is important. The pressure difference is termed “deformation pressure” by Nims.[13]

Spacesuit

One can reduce the ΔP in Eq(1) and, therefore, the P(DCS) by reducing P_i or increasing P2, or some combination of both to achieve acceptable risk and operational efficiency. In our application, P2 is suit pressure. The fascinating history about the development of U.S. and Russian spacesuits and the selection of suit pressure for particular missions is beyond the scope of this report to summarize. As the spacesuit is a flexible spacecraft, details about spacesuits are available from Hoffman[14] and Flugel et al.[15] Current suit technology, especially in the design of gloves, does not permit a high-pressure suit without increased fatigue and reduced mobility. So,

References 3-10.

reducing the risk of DCS by increasing suit pressure has significant operational limitations, and there is significant overhead and reward when considering a spacesuit that operates over a range of pressures.

A balance must be achieved in each application between the cost to reduce P_i and the cost to increase P2, not just the cost in dollars but also the cost in operational efficiency. At 1 extreme in Apollo and Skylab, P_i was reduced to such an extent that the lowest pressure in the suit (A7L and A7L-B) was set just to avoid significant hypoxia, with some margin for error. In contrast the P_i in the shuttle, *Mir* space station, and ISS could not be reduced without significant denitrogenation time. To achieve a balance between acceptable risk and operational efficiency, P2 in the shuttle extravehicular mobility unit (EMU) was set higher than it was in Apollo and Skylab spacesuits with DCS and not hypoxia as the dominant concern.

Spacesuits are not the only pressure garments used by NASA. A modified U.S. Air Force (USAF) U-2/SR-71 partial pressure garment was used during early flight testing of the shuttle. Astronauts launched through and reentered the atmosphere under shirtsleeve conditions after the flight testing and before the *Challenger* accident. Following the loss of *Challenger*, a partial-pressure launch entry suit was developed that later became the full-pressure advanced crew escape suit, which protects astronauts from inadvertent rapid depressurization during launch and reentry. Pilots who fly the WB-57 as part of the High Altitude Research Program at JSC are protected from hypoxia and DCS in the event of inadvertent cabin depressurization by wearing a pressure garment and by breathing 100% oxygen (O_2) prior to and during all phases of the flight.

Denitrogenation

Much of what we know about denitrogenation and hypobaric DCS was learned during and shortly after World War II (WWII) and is available on the pages of Fulton's 1951 book[16] *Decompression Sickness*,[17,18] with additional information in the 4th edition of *Fundamentals of Aerospace Medicine*[4] and *The proceedings of the 1990 hypobaric decompression sickness workshop*.[19] The advent of Doppler ultrasound bubble detection technology in the 1970s provided a significant tool to increase our understanding of DCS. Clearly, denitrogenation protocols are effective in reducing the P(DCS) and the severity of symptoms, as well as the potential for venous gas emboli (VGE) and arterial gas emboli (AGE). After denitrogenation, also called O_2 prebreathing, an astronaut has a small amount of tissue nitrogen (N_2) to manage as compared to a diver who enjoys even 2 modest SCUBA dives. But, in most cases, the astronaut depressurizes to a low-pressure spacesuit while the diver returns to sea-level pressure. The amount of dissolved N_2 that transforms into evolved gas under a modest supersaturation after a prebreathe (PB) must be very small for the astronaut, but the volume expansion (Boyle's Law) at the new lower pressure is potentially larger for the astronaut than it is for the diver.

Human gender differences ensure a wide range of body types. A brief comparison using gender illustrates that no 2 people have the same quality or quantity of N_2 elimination (washout) and uptake (washin). Table 1 shows the estimated volume of N_2 dissolved in lean and fat tissues in a representative male and female. The total volume of N_2 is slightly more in the woman than in the man, given an N_2 solubility coefficient of 0.0146 ml (standard temperature [0°C], pressure (1 ATM), and dry gas [STPD]) N_2/ml tissue * ATM N_2 in lean (aqueous) tissue and 0.0615 ml N_2/ml tissue * ATM N_2 in fat (lipid) tissue, and the other information in the table.

Table 1. Estimated N_2 Content by Gender

gender	wt (kg)	body fat% (% total wt)	fat mass (kg)	N_2 volume in fat (ml)*	lean mass (kg)	N_2 volume in lean (ml)	total N_2 volume (ml)
male	75	10	7.5	405	67.5	778	1183
female	60	25	15.0	809	45.0	519	1328

*Density of fat = 0.9 kg/liter, partial pressure of N_2 = 0.79 ATA in breathing air, and total body weight was not reduced to compensate for the weight of inert bone.

What is apparent is that the amount of N_2 in the fat tissues of the woman is twice as great as that in the man, and that the amount of N_2 in lean tissues of the man is slightly greater than in the woman. Given enough PB time, the same total volume of N_2 would be removed from both the man and the woman. As PB time is always limited, the kinetics of N_2 elimination and the relative contributions of N_2 from the fat and lean tissues during a limited PB must be considered.

During the early phase of a PB, a large amount of N_2 is eliminated from a well-perfused and large lean tissue reservoir in the male, with a lesser amount of N_2 coming from a poorly perfused fat depot that is smaller than that in the woman. Although poorly perfused fat contributes some N_2 throughout the PB, it is likely responsible for the long tail of a typical N_2 elimination curve. The female also provides a large amount of N_2 that was initially removed from a well-perfused but smaller lean tissue reservoir, with a greater amount of N_2 than in the man coming from a poorly perfused fat depot that is larger than in the man. This poorly perfused fat tissue has 5 times greater affinity for N_2 than does the well-perfused lean tissue. As a result, a large amount of N_2 is available from fat tissue in the woman, and the N_2 slowly leaves the body during PB so that you would expect an even longer tail on a typical N_2 elimination curve for women than on a typical N_2 elimination curve for men.

It is important to define the minimum PB time that protects the greatest number of EVA astronauts, whether they are male or female and given a reasonable range of body type. It is important to keep the PB procedure simple and to balance the risk of DCS with available treatment resources.[20] Risk is defined as the P(DCS) and the consequence of DCS. Since the consequence of a serious case of DCS in space is high, the P(Serious DCS) must be very low to achieve an acceptable operational risk.

Operational Denitrogenation

A minimum 3-hr in-suit PB was performed before launch in all NASA programs except that for the shuttle.[21] This protected inactive astronauts from DCS after reaching orbit; during ascent cabin pressure was reduced from 14.7 to 5.0 psia and atmosphere was simultaneously enriched to 100% O_2.[1] Although this PB was effective in most cases, 1 astronaut wrote, years after leaving the space program, that he had symptoms consistent with DCS while at 5.0 psia. Michael Collins on Gemini X and later on Apollo 11 believed he had symptoms of pain-only DCS in his left knee that eventually resolved in the 100% O_2 atmosphere as the missions proceeded.[22] This was not an unexpected outcome based on prior PB validation trials reported by Maio et al.[21,23] Astronauts on subsequent EVAs from the Apollo spacecraft and Skylab, and on moon walks from the Apollo lunar module, who were wearing suits pressurized to 3.7 psia were not at risk for DCS due to denitrogenation during their extended time in the hypobaric and hyperoxic breathing environment. However, the increased risks of fire and atelectasis on long missions, as well as many other considerations, compelled NASA to select an Earth-normal atmosphere for the shuttle and the ISS. The Russian

space program had already committed to an Earth-normal atmosphere, even before the *Mir* space station was launched. A consequence of these decisions was that EVAs in the 4.3-psia EMU and the 5.8-psia Russian Orlan spacesuit could result in DCS, so efficient and effective denitrogenation protocols were needed. Compounding the challenge is that an air break (a brief exposure to high partial pressure of N_2 [ppN_2]) during a 100% O_2 PB is a real possibility so procedures are needed to compensate for air breaks.

In-suit

Shuttle astronauts have two denitrogenation strategies available to reduce the P(DCS). In the first denitrogenation strategy, the astronaut simply breathes gas, often through a mask or in a spacesuit, with enriched O_2, often 100% O_2, for a time period depending on the hypobaric exposure pressure, often the spacesuit operating pressure. The type and amount of work done in the suit and the duration of hypobaric exposure set the final PB time to achieve an acceptable risk of DCS.[24] The operational challenge is to match the length of the PB with an acceptable low incidence of DCS[25] to produce an efficient EVA system. Waligora et al[26] describe tests of 3.5- and 4-hr PBs at JSC. The first of several PB protocols were evaluated with male volunteers in August 1982, and DCS after the first 3.5-hr PB was reported in a subject and a Doppler technician.[27,28] This was an inauspicious start to the validation of a 3.5-hr PB. A 4-hr PB reduced the incidence of DCS from 42% to 21% and the incidence of VGE from 71% to 46% in data normalized to a 6-hr exposure to 4.3 psia in men that ambulated as part of exercise at 4.3 psia.[26,28] On April 12, 1981, the shuttle STS became a reality. The first EVA from the shuttle was performed on April 7, 1983, using a 3.5-hr baseline in-suit PB. Only 3 two-person EVAs have been performed from the shuttle after a 3.5- or 4-hr in-suit PB since April 1983. The 4-hr in-suit PB remained an option throughout the shuttle program, however. What appeared to be a simple in-suit PB protocol was not as acceptable as the shuttle staged protocol, described below.

Shuttle Staged

Ambient pressure is decreased to an intermediate pressure in the second denitrogenation strategy so the inspired partial pressure of N_2 (P_IN_2) is lower than the initial P_IN_2.[21,29-32] The staged depressurization approach is enhanced when O_2 concentration is also increased to lessen the impact of hypoxia and to further reduce P_IN_2. However, the initial pressure reduction likely transforms a subpopulation of tissue micronuclei into “silent” bubbles in some astronauts, so a 60-min PB with a mask is performed before the initial modest reduction in ambient pressure to 10.2 psia occurs.[11,26,33-35]

The cumulative fraction of VGE first detected in subjects exposed to 4.3 psia for 4 hr after 3 different PBs is shown in Figure 1. A related figure appears in Waligora et al[26] (their Figure 12). All subjects performed EVA-simulation work activities and were ambulatory at 4.3 psia. The solid line (steps) that increases and plateaus quickly to about 45% is from 10 of 22 subjects who had a mean VGE onset time of 43 ± 43 min standard deviation (SD). This trial did not include a 1-hr PB before a 12-hr stay at 10.2 psia where subjects breathed 26.5% O_2. The dashed line that plateaus to about 50% VGE is from the same trial as described above except it did include a 1-hr PB before the ascent to 10.2 psia. The mean VGE onset time in 18 of 35 subjects with VGE was 105 ± 48 min. Finally, the dashed line that plateaus to about 65% VGE was from a trial with a 3.5-hr PB and a direct ascent to 4.3 psia. The mean VGE onset time in 15 of 23 subjects with VGE was

115 ± 55 min. The mean VGE onset times were statistically longer ($p<0.002$) as compared to the trial without the 1-hr PB before ascent to 10.2 psia for 12 hr.

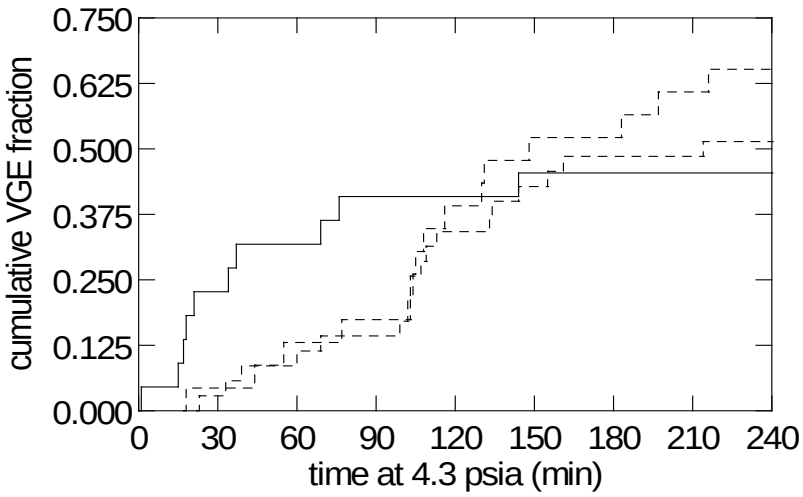

Figure 1. Onset time for first detection of VGE was earlier in a trial (Test 2b) in which no PB was done before the first ascent and subsequent 12-hr exposure to 10.2 psia (solid line) compared to when a 1-hr PB was performed (50% peak, Test 3b) or when there was a direct ascent to 4.3 psia after a 3.5-hr PB (65% peak, Test 2a). Data for Test 3b are from 4 hr of a 6-hr exposure.

The computed decompression dose (described later) was slightly higher in the trial that omitted the initial 1-hr PB, so a high group incidence of VGE was expected. Instead, a rapid onset of VGE was observed in a few subjects, possibly because micronuclei associated with the vascular endothelium transformed into silent bubbles that were ready to grow and enter the venous circulation after final depressurization to 4.3 psia. An ascent to only 10.2 psia (3000 m [9750 ft]) without some PB predisposed some subjects to produce VGE shortly after reaching 4.3 psia, even after spending 12 hr at 10.2 psia with a 40-min PB before the final ascent to 4.3 psia. It is notable that 5 of 10 subjects in this trial had VGE first detected within 30 min at 4.3 psia. One subject had VGE detected after 1 min at 4.3 psia and at 65 min had signs and symptoms classified as serious DCS. DCS was diagnosed in all 3 trials, about a 20% group incidence and a mean onset to first symptoms of about 2 hr.

Optimization of the final shuttle 10.2-psia staged depressurization protocol took months of planning and years of validation. The first critical step was to certify the shuttle for operations at a reduced pressure with an enriched O_2 atmosphere, since the vehicle was not planned to operate under these conditions. Several interacting variables were evaluated in isolation or combination: rate of ascent to intermediate pressure, the intermediate pressure itself (equipment cooling issues[36]), the partial pressure of O_2 and ppN_2 at the intermediate pressure (hypoxia and flammability issues[37]), length of stay,[32,33] likelihood of silent bubbles, final suit pressure, duration of EVA, work performed in the suit, final in-suit PB time before final ascent, and balancing the acceptable risk of DCS during EVA with limited treatment options.[26,38]

The protocol that ultimately became the preferred PB for shuttle was achieved in 3 steps as follows: (1) an initial 60-min PB by mask, of which 45 min were completed before the shuttle atmosphere was depressurized from 14.7 to 10.2 psia and the air was enriched to 26.5% O_2 to provide an inspired partial pressure of O_2 (P_IO_2) of 127 mmHg; (2) a minimum stay of 12 hr at this intermediate pressure; and finally (3) an in-suit PB before a final depressurization to 4.3 psia, lasting 40 to 75 min depending on the time spent at 10.2 psia. The time at 10.2 psia, which was not spent on a mask, was not a break in PB since the lengthy exposure to a reduced ppN_2 at 10.2 psia, approximately 7.5 psia, continued the denitrogenation process. Astronauts simply donned their suits at 10.2 psia when they were ready and performed a final 40- to 75-min in-suit PB before final depressurization to 4.3 psia, without the need to first re-pressurize to 14.7 psia. If the time spent at 10.2 psia was greater than 36 hr, the initial 60-min mask PB at 14.7 psia was omitted. The rationale for this was that any silent bubbles formed during the 15- to 20-min depressurization to 10.2 psia would be reabsorbed given enough time at 10.2 psia. This procedure was therefore complicated and had several operational and physiological impacts, and yet it was preferred over a simple in-suit PB. The first EVAs that used the shuttle staged protocol were on STS-41B in February 1984, and the last of about 180 person-EVAs is expected to take place in 2011 with the retirement of the shuttle.

International Space Station Campout

A modification of the shuttle protocol, which is called the campout protocol, is now used on ISS. Since the entire atmosphere in the ISS cannot be reduced to 10.2 psia and enriched to 26.5% O_2, 2 astronauts must "camp out" at 10.2 psia in the ISS airlock. For various operational reasons the time at 10.2 psia is limited to 8 hr and 40 min, most of which is spent sleeping. The lack of food preparation and rest room facilities in the airlock means that a re-pressurization to 14.7 psia is needed once while 2 astronauts breathe 100% O_2 by mask for 70 min. On return to 10.2 psia the masks are removed and the suit-donning process is completed. The airlock is re-pressurized to 14.7 psia after the astronauts don their spacesuits to allow an assistant to exit at 14.7 psia and to complete the 50-min in-suit PB before final depressurization of the airlock to the vacuum of space. After extensive review, the similarity of the campout PB to the shuttle staged PB along with good operational experience with the shuttle PB negated an empirical validation of the campout PB. The first EVAs from the ISS using the campout protocol took place in September 2006 with about 140 person-EVAs completed by the end of 2010.

Why were these complicated staged PB procedures favored over a simpler in-suit PB? The use of the staged protocol reduces fatigue in astronauts, who would otherwise be in the spacesuit for 10 to 12 hr, and increases the efficiency of the astronauts, since time that would otherwise be wasted in the suit during the PB can be spent on other tasks. The only way to reduce fatigue and maintain efficiency while using the in-suit PB is to perform most of the PB while using a mask outside of the suit, but this eventually requires a transition from the mask to the suit. Since the suit requires a 100% O_2 purge and leak check, the transition from a mask, or even a mouthpiece and noseclip, to the suit with 100% O_2 without an air break has proven problematic.

Exercise Prebreathe for the International Space Station

After the ISS airlock was delivered on STS-104.7A in July 2001 and before the campout protocol was available in September 2006, an option to perform exercise-enhanced denitrogenation from the ISS became available. Since the elimination and uptake of N_2 is a perfusion-limited

process, the use of exercise during the PB is a third denitrogenation strategy. An accelerated denitrogenation protocol was needed to avoid scheduling constraints on EVAs performed from the ISS. The ambitious goal was to reduce the available 4-hr resting in-suit PB by about half. Before the delivery of the Quest airlock, EVAs to support ISS construction were performed with hatches closed between the 2 vehicles so that shuttle 10.2-psia PB could be used. The first use of exercise PB was to complete the installation of the ISS airlock. The discomfort and complexity of adding an effective interval of exercise during PB must be balanced with the rewards (less total PB time and greater reduction in the P(DCS) from an alternative resting PB) or the option is not acceptable to the astronaut. No single, reasonable, short-term intervention can increase cardiac output as much as exercise. Exercise during PB was evaluated during and shortly after WWII[39-41] and reevaluated at Brooks Air Force Base (AFB) for the special operations community[42-47] and most recently by NASA. Details are available about 9 exercise PB options evaluated by NASA from 1997 to 2009[48-51] (also see Table 2).

Table 2. Summary of DCS and VGE in Tests from 1982 – 2009

Test	P2 (psia)	conditions	number m	number f	mean age	DCS	VGE (any Grade)	VGE (Grade IV)
1a	4.3	P	11	0	34.5	4	7	4
1b	4.3	S	13	0	32.3	3	11	7
1c	4.3	S	12	0	32.0	4	7	6
1d	4.3	S	3	0	39.6	2	3	2
2a	4.3	P	23	0	31.6	7	15	8
2b	4.3	S	22	0	31.5	6*	10	7
3a	4.3	P	28	0	31.0	6	13	11
3b	4.3	P,S	35	0	30.1	8	20	8
3c	4.3	P	14	0	32.5	3	5	1
3d	4.3	P,S	12	0	28.5	2	5	2
4a	4.3	P,S	12	0	30.1	1	7	3
4b	4.3	P,S	12	0	30.1	0	2	1
4c	4.3	P,S	12	0	30.1	0	4	1
4d	4.3	P,S	12	0	30.1	0	0	0
4e	4.3	P,S	12	0	30.1	0	4	1
4f	4.3	P,S	12	0	30.1	0	0	0
5a	4.3	P	19	19	31.5	4	11	4
5b	4.3	P	11	0	32.0	0	0	0
6	6.0	S	15	14	32.9	1	3	0
7a	6.5	direct ascent	11	0	28.2	4†	8	6
7b	6.5	direct ascent	11	0	28.2	2	8	4
8a	6.5	direct ascent	29	11	32.5	7	20	13
8b	6.5	direct ascent	30	11	32.6	10*	22	17
9a	6.5	direct ascent	15	9	32.1	1	12	7
9b	6.5	A	14	9	33.8	2*	6	1
9c	4.3	A	9	2	34.8	3	5	4
9d	4.3	A	6	1	36.4	0	2	0
9e	4.3	E,A	7	0	34.6	0	2	0
10	10.1	FAD	14	5	31.7	1	6	3
11a	4.3	P,A	16	12	33.2	3	9	4
11b	6.5	direct ascent	1	3	39.5	0	1	0

Test	P2 (psia)	conditions	number m	f	mean age	DCS	VGE (any Grade)	VGE (Grade IV)
Phase I	4.3	P,E,S,A	33	14	29.1	9	23	2
Phase II	4.3	P,E,S,A	35	10	31.7	0	14	3
Phase IV	4.3	P,E,S,A	44	12	30.1	8	23	7
Phase V-1	4.3	P,E,A	7	2	31.5	3	5	2
Phase V-2	4.3	P,E,A	1	2	39.2	1*	3	2
Phase V-3	4.3	P,E,A	38	10	36.9	7	25	5
Phase V-4	4.3	P,E,A	3	3	31.5	3	3	1
Phase V-5	4.3	P,E,S,A	37	11	32.3	2	14	8

Conditions: P, some PB occurred before ascent; S, a portion of the PB was spent at 10.2 psia breathing 26.5% O_2; A, subjects were "adynamic" (no ambulation before or during the altitude exposure); E, a prescribed exercise was performed during some interval of the PB; and FAD, flying after diving.
*One case was classified as Type II DCS; †2 cases were classified as Type II DCS.

Two exercise PB protocols that are deemed acceptable for operations on ISS are briefly described. The first of these is the Exercise PB protocol, which uses the cycle ergometer with vibration isolation and stabilization (CEVIS) device; and the second of these is the In-suit Light Exercise (ISLE) PB protocol, which employs the EMU as a resistive exercise device.

For the Exercise PB protocol an astronaut, months before launch, performs a peak O_2 consumption test (VO_2 peak test) using leg ergometry, and a linear regression of O_2 consumption vs. watts (workload) is created. An exercise prescription is produced that distributes the appropriate workload between the upper body (12%) and the lower body (88%). Before performing an EVA the astronaut breathes O_2 from a mask and performs 3 min of incremental exercise on the CEVIS at about 75 rpm using a prescription that increases work from 37.5%, to 50.0% and then to 62.5% of the VO_2 peak while also rhythmically pulling against elastic surgical tubing to include upper body activity (see Figure 2). The ergometry is completed after 7 min at 75% of VO_2 peak. After waiting an elapsed time of 50 min while still breathing 100% O_2 from the mask, the astronauts and an assistant depressurize to 10.2 psia in 30 min in the ISS airlock. During this depressurization, the liquid cooling garment and the lower portion of the spacesuit are donned by the astronauts. Once the airlock O_2 concentration stabilizes at 26.5%, the astronauts and the attendant remove the masks and complete donning the upper torso of the spacesuit. Thus, for a good portion of the PB time, the astronaut is actively engaged in the suit-donning process. A leak check and then purge with 100% O_2 to remove N_2 from the suit completes the suit-donning procedure. In-suit PB starts in conjunction with a 5-min re-pressurization back to 14.7 psia where the remaining 55 min of in-suit PB are performed and the assistant exits the airlock. The final depressurization to 4.3 psia in the suit and to the vacuum of space takes 30 min.

For the ISLE PB protocol, the astronaut does not engage in a short bout of intense PB exercise on the CEVIS prior to suit donning at 10.2 psia but instead performs a longer bout of mild exercise in the EMU. The ISLE PB protocol shares many steps with the Exercise PB protocol but differs from the latter in that 40 min are spent breathing 100% O_2 by mask followed by a 20-min depressurization to 10.2 psia. Once the astronaut has completed suit donning, arm and leg motions are performed for 4 min followed by 1 min of rest in conjunction with a 5-min re-pressurization back to 14.7 psia. The mild exercise pattern continues for 50 min and achieves a minimum O_2 consumption of 6.8 $ml*Kg^{-1}*min^{-1}$. An additional 50 min of rest completes the PB protocol followed by a 30-min depressurization of the airlock to vacuum.

The return to 14.7 psia after a short suit-donning period at 10.2 psia in both the Exercise and the ISLE PB protocols and 2 returns to 14.7 psia over the course of the longer campout PB likely

reduced the subsequent P(DCS) by removing silent bubbles. These bubbles had the potential to form from a limited number of large-radius micronuclei (see **Micronuclei**) during the initial depressurization to 10.2 psia. After the bubbles are formed and are then reabsorbed during the repressurization to 14.7 psia while breathing 100% O_2, tissues are temporarily left with a smaller range of micronuclei radii from which to grow bubbles during the final depressurization to 4.3 psia. Recall that the shuttle 10.2-psia staged depressurization protocol did not require a return to 14.7 psia to remove an assistant from the airlock. Since the entire habitable volume of the shuttle was depressurized, the astronauts simply continued the depressurization from 10.2 to 4.3 psia after suit donning in the airlock.

Figure 2. Michael Gernhardt (right) performs equipment and procedures checkout of the Exercise PB protocol during STS-104.7A with assistance from Charles Hobaugh. This procedure was first used on July 20, 2001, during the third and last EVA of the mission.

An advancement in denitrogenation protocol selection came via establishing prospective accept conditions for validation trials. A sequential design was used to good effect by Kumar et al[52] as a means by which to discontinue a trial when statistical significance was achieved, thus minimizing risk to research subjects. A sequential design concept was also applied to the PB protocol selection for the ISS. First, an assessment of the maximum impact that a case of DCS would have on the completion of ISS assembly, balanced with an ability to effectively treat DCS

on orbit, created 3 "accept" conditions for validation trials. A PB protocol was acceptable in validation trials for ISS EVA operations if no serious case of DCS was observed, if the incidence of pain-only DCS was ≤15%, and if the incidence of Grade IV VGE (described later) was ≤20%.[48] Second, the "accept" region during sequential trials was set at 95% statistical confidence with the "reject" region set at 70% statistical confidence, which avoided continued testing of ineffective protocols. In 9 exercise-enhanced PB protocols,[50] in 50 exposures the observed DCS could not exceed 3 cases (6%) and the observed Grade IV VGE could not exceed 5 cases (10%) to meet the accept conditions. One of 9 trials (Phase II) had no DCS with only 3 occurrences of Grade IV VGE in 45 exposures that combined short-duration, high-intensity exercise with additional light exercise during the PB. Another trial (Phase V-5) had 2 cases of Type I DCS with 8 occurrences of Grade IV VGE in 48 exposures that combined long-duration, low-intensity exercise. These protocols were acceptable to NASA after extensive peer review of the research and with the realization that implementation of an operational PB is always more conservative than the tested PB. Thirty-four person-EVAs have been conducted from the ISS after use of the Exercise PB protocol. The first scheduled use of the ISLE PB protocol is during the last shuttle mission (STS-134). The ISLE PB protocol is available for subsequent EVAs from the ISS.

Air Break During Prebreathe

Various methods to preserve the quality of and confidence in the PB during the transition from mask to suit were evaluated at JSC, and all were found to be inadequate. In effect, the inability to avoid a potentially long air break in PB at 14.7 psia and ignorance of the consequences of an air break during PB were responsible for the development of the staged denitrogenation protocols on the shuttle and the ISS.[1,31] The few research studies that exist concerning break in PB are listed in chronological order in the footnote.[†]

A lengthy break in PB is an operational reality that could compromise an otherwise safe denitrogenation procedure and jeopardize a scheduled EVA. The NASA Aeromedical Flight Rules defines O_2 payback time based on the location and duration of a simple air break during a PB. Payback time is the number of minutes of additional PB time needed to compensate for an interruption in the original PB time. For air breaks during resting PB, the payback time on 100% O_2 is 2 times the duration of the air break and 4 times the duration of the air break if the air break occurs early in the Exercise PB protocol for the ISS. A break in PB that lasts longer than 10 min requires that the PB be repeated from the start, or the crew switch to an alternative PB. A notable case of a complicated break in PB occurred during preparations for the second of 3 EVAs on STS-129. A mechanical problem in the airlock control panel on the ISS occurred about 2 hr into the sleep period of the campout PB. This failure initiated a re-pressurization of the airlock. There was no reasonable recovery from this air break due to the time needed to reconfigure the airlock operations. The decision was made to switch to Exercise PB, which was completed the following day and preserved the original scheduling of the second EVA.

Estimates for PB payback time have ranged from 1[54] to 35 times (Adams et al)[55] the duration of the air break. Unfortunately, no published results exist that can be confidently applied to NASA operations. There are simply no data about payback time if PB is interrupted during exercise. Simple rules for PB compensation after an air break are desirable for space EVA operations, but no 2 people have identical N_2 uptake and elimination kinetics, and in reality the duration of the break, the point at which the interruption in the PB occurred, and the remaining amount of PB time

[†]*References 17, 53-59.*

are infinitely variable. Breathing 1 ATA of O_2 is known to decrease cardiac output and increase peripheral vascular resistance by increasing vasoconstriction.[60,61] It is reasonable to suppose asymmetrical N_2 kinetics as a consequence of an air break. It is also reasonable to suppose that there is a change in the size distribution of tissue micronuclei as a function of the O_2 window during the PB[62] and the size distribution is influenced by air breaks. So, simple payback rules may not suffice under all conditions, and a quantitative approach to access payback time is a goal for the future.[63] Data from Pilmanis et al[59] showed that a 10-min air break taking place 30 min into a 60-min PB prior to a 4.37-psia exposure did reduce the mean time to onset of symptoms and did increase DCS incidence at 1 hr compared to controls.

Tissue Ratio as Decompression Dose

Fundamental to our understanding of the P(DCS) in astronauts is to first understand how we calculate a tissue ratio (TR). TR is a simple index of decompression dose, first used at the turn of the century by Haldane, that defines the limit to direct ascent for divers. (See Stepanek and Webb[4] for historical background on TR.) A decompression dose can also be computed from a biophysical model that addresses bubble growth, such as the maximum size a theoretical bubble achieves, the rate of growth of that bubble, or the summed volume from a collection of bubbles competing for inert gas.[64,65] TR is the ratio of computed $P1N_2$ in a theoretical tissue to ambient pressure. Equation (2) defines $P1N_2$ and P2 as the ambient pressure after depressurization. Pre-breathing 100% O_2 or O_2-enriched mixtures before a hypobaric exposure prevents DCS, so it is necessary to account for the use of O_2-enriched mixtures as part of the expression for decompression dose. After ppN_2 in the breathing mixture changes, such as during a switch from ambient air to a mask supplied with 100% O_2, the ppN_2 that is reached in a designated tissue compartment after a specific time is $P1N_2$:

$$P1N_2 = P0 + (P_a - P0)\,(1 - e - k\,t\,), \qquad (2)$$

where $P1N_2$ is calculated for the tissue after t min, P0 is the initial ppN_2 in the compartment, Pa is the ambient ppN_2 in the breathing mixture, and t is the time at the new Pa in minutes. The TR constant k is equal to $\ln(2)/t_{1/2}$, where $t_{1/2}$ is the half-time for ppN_2 in the 360-min compartment. The particular half-time compartment is a statistical construct that optimizes TR as a decompression dose to the observed dichotomous DCS or VGE outcomes from a collection of trials.[66] A long 360-min half-time is associated with long PB times tested by NASA.[67] A shorter half-time combined with long PBs produces low TRs that are not consistent (optimized) with trials that yield significant DCS and VGE incidence. The half-time compartment is simply a surrogate linked to the actual process at the tissue level that dictates the true evolved gas condition.

Equation (2) describes the simple case in which P_a changes instantaneously, a step-change. This form is sufficient in most applications since donning or removing an O_2 mask changes P_a within a few breaths. There is also the possibility that P_a changes through time, such as breathing air during a long depressurization, or changing the N_2 content through time at some intermediate pressure. An expanded form of Eq(2) covers these cases. One novel application is to reduce N_2 content through time as dictated by the operational timeline such that $P1N_2$ is appropriate at the time of suit donning, thus avoiding a final in-suit PB period. This application requires an automated control system to change the breathing atmosphere through time and space within a vehicle that is compatible with enriched O_2. As the cost likely exceeds the rewards with this approach, it has not been pursued. Finally, Eq(2) is modified to compute $P1N_2$ to account for

intervals of exercise during PB. The tissue rate constant k is defined in terms of $\%VO_2$ peak during the PB.[50]

Equation (3) is 1 form of TR as decompression dose, which approximates the potential volume at an ambient pressure of N_2 evolved in a unit volume of tissue given that all available N_2 at P2 has transformed from the dissolved state to the evolved state:[68,69]

$$\text{decompression dose} = [(P1N_2 / P2) - 0.79], \quad (3)$$

where decompression dose is 0 at sea level since [(11.6/14.7) – 0.79] is 0.

TR, which is an index of the true decompression dose, is fundamental to other formal expressions of decompression dose as evolved gas. Given an abundance of quality research data, the bottom of the S-shaped curve on a DCS vs. TR dose-response curve would be nearly flat over a range of TR to, say, 1.1. The flat region is an indication that a decompression dose must exceed some critical value. TR is utilitarian, as it easy to use in statistical regression models to describe DCS and VGE outcomes from combined research trials over a range of TRs. TR, or R-value in NASA terminology, becomes a number that cannot be exceeded. For example, an R-value of 1.65 or less is acceptable for EVA operations in the 4.3-psia EMU from the shuttle. An R-value of 1.65 in an EMU does not mean the P(DCS) is 0.[28,70] Risk and reward must be balanced to achieve an operational protocol, and finding this balance is as much an art as a science. Operations using the Russian Orlan spacesuit at 5.8 psia result in an R-value of about 1.85 to provide a P(DCS) that is the equivalent of the P(DCS) in the EMU, so the acceptable R-value (TR) is not an absolute but a function of suit pressure.[67,71] DCS research and operational EVA experience in the Russian space program is too extensive to summarize here (Barer[72]) and parallels the efforts in the U.S. space program.

Micronuclei

The previous discussion focused on the classic Haldanean approach: reducing the amount of tissue N_2 to limit bubble growth. But, an emerging area of DCS prevention is also to hinder the transformation of tissue micronuclei into growing bubbles.[64,73] The presence of gaseous micronuclei in the tissues permits DCS under modest depressurizations.[74] Information about and evidence for tissue micronuclei come mostly from indirect observations. Application of a high-pressure spike, either hydraulic or pneumatic, filtration, or ultracentrifugation of a sample are all accepted means to reduce the number and size of micronuclei (change the distribution), as is evident from fewer bubbles or cases of DCS after a subsequent depressurization.[75-77] One inference from these studies is that normal activity establishes a size distribution of micronuclei within tissues that can be modified by changing your activity. The idea of "using up" micronuclei faster than they are generated as a means to understand increased resistance to DCS on repeated exposures has also been discussed.[78] A comprehensive review and discussion of micronuclei is not provided here, but information is available in various sources.[‡]

If micronuclei are considered if the results from research on DCS are then applied to astronauts who perform EVAs, walking in an altitude chamber is not a reasonable analog to walking in space.[80,88,89] Exercise increases the risk of DCS, generally in the limb performing the exercise.[24,90-92] Walking is such a natural event that in research on DCS it is frequently ignored as being exercise. This simple and ubiquitous act has new relevance as humans venture into space

[‡]*References 78-87.*

and ambulate on the moon and later Mars, especially as it relates to the risk of DCS. Calling an EVA in μ*g* from the shuttle or ISS a spacewalk is a misnomer. Astronauts do not ambulate in the conventional sense but only anchor their legs to a stable structure so the upper body can effect some task. Powell coined the term "adynamia" to characterize the lack of movement and, thus, of dynamic forces in the lower body (lower body adynamia) over several days of adaptation to μ*g* and during EVAs.[81,93-95]

The fundamental premise of adynamia concerns the control of nucleation processes within tissues and fluids. In the absence of supersaturation, the spontaneous rate of nucleation is inconsequential when micronuclei on the order of microns in radius are considered. The number or distribution of micronucleus sizes can be influenced, however, before supersaturation exists when mechanical energy is added to the system. It is notable that subjects who performed brief but vigorous dual-cycle (arms and legs) ergometry at the start of an exercise PB showed earlier VGE onset compared to those who performed ergometry about 15 min into the start of the PB.[50] A 15-min delay in starting the ergometry in a 150-min total PB time delayed VGE onset time in research subjects during a subsequent exposure to 4.3 psia. Astronauts always perform EVAs in pairs, so those who use the Exercise PB protocol start the PB at the same time, but someone must go first as there is only 1 leg ergometer on the ISS dedicated to this protocol.

Violent muscular contractions in bullfrogs before a hypobaric exposure[96] were associated with bubble formation in resting animals while at altitude. The number of bubbles was reduced if the bullfrogs were allowed to recover for as long as 1 hr after electrical stimulations. The authors offered 2 explanations for this: a short-lived local increase in carbon dioxide (CO_2) that facilitated bubble growth at altitude, or the inception of micronuclei or some other short-lived entities that would later facilitate the growth of bubbles at altitude. This concept was tested in humans[97] when 20 subjects were exposed to 6.2 psia on 3 separate and random occasions without the confounding of PB or any exercise at altitude during a 2-hr exposure. Each subject performed 150 deep-knee flexes in 10 min, either 2 hr, 1 hr, or just prior to ascent, with the remaining time spent adynamic in a chair. It was hypothesized that exercise before decompression would generate a population of some entity (micronuclei, macronuclei, vapor-filled cavities trapped on vascular endothelium, or increase the concentration of CO_2) that would diminish in size or concentration given enough time before ascent. The investigators used subsequent VGE information to indirectly test the hypothesis. They observed that intense lower-body activity just before the altitude exposure did cause more VGE to appear and to cause the VGE to appear earlier than when exercise was done earlier. The critical observation was that the predisposing factor(s) diminished with time while subjects sat quietly in a chair before the ascent.

If DCS outcome is related only to tissue N_2 supersaturation, perhaps the decrease in P(DCS) tracks the decrease in computed supersaturation. If the relationship is not a mirror image, perhaps factors other than N_2 supersaturation are jointly responsible. The dashed line in Figure 3 is from the natural logarithm transformation of the exponential decay in a 360-min half-time compartment that is normalized by dividing the initial tissue N_2 pressure by 11.6 psia, ambient ppN_2 at sea level. The solid curve is the same transformation applied to the P(DCS) from a survival model[67] evaluated over 6 hr of PB given that the person performed mild exercise at 4.3 psia for 4 hr while breathing 100% O_2 through a mask. Other factors that dictate the DCS outcome must exist besides tissue N_2 supersaturation or the 2 plots would look similar. If DCS outcome is a complex competition between potential for evolved gas and transformation of micronuclei into bubbles, it might be expected that the curves for log[P(DCS)] and log(normalized N_2 pressure) would diverge over a range of PB time.

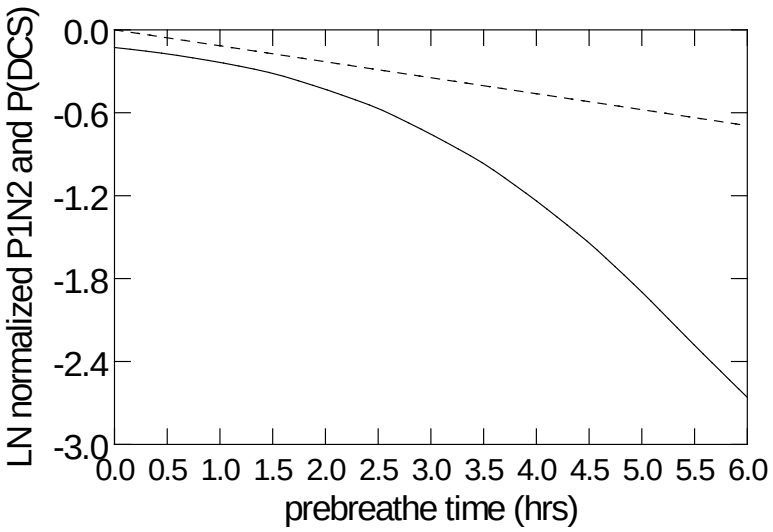

Figure 3. Change in computed tissue N_2 pressure (dashed curve) and P(DCS) (solid curve) as a function of PB time, under conditions of the simulation described in text.

The physics of micronucleus stability, creation, size distribution, absolute numbers in tissues, and transformation into growing bubbles for a given N_2 supersaturation must be complex.[98-100] One could hypothesize that only a few large-radius micronuclei could be absorbed during a short 100% O_2 PB, and that more large- and small-radius micronuclei are absorbed after more than 90 min of PB. There would come a point during a long PB in which fewer and smaller-radius micronuclei exist to transform subsequently into growing bubbles under the prevailing reduced N_2 supersaturation, as suggested by the rapid decrease in ln[P(DCS)] after 3 hr of PB in the survival model (Figure 3). The reality of bubble growth in tissue is that it is not just the absolute potential for evolved gas, as reflected in an exponential washout curve, but is a competition between the potential for available gas and the population of micronuclei that are available to accept the excess gas and transform into growing bubbles. The acceptance of this excess gas occurs through simple diffusion, but that is the only simple statement possible.

The classic soda-bottle analogy of bubbles in the body illustrates the physical consequence of depressurization, but emerging science suggests that activation of various stress-induced biomolecules before, during, or after depressurization will influence DCS and VGE outcomes.[101,102] Astronauts routinely take aspirin and other pharmacological agents to manage the stress of space flight, which may influence the DCS and VGE outcomes. The benefit of particular exercise before and during PB likely has a biochemical component that is incorrectly attributed to enhanced N_2 elimination. The large surface area of the vascular endothelium and its interaction with stress-induced biomolecules offers an opportunity to understand how excess intracellular dissolved gas actually becomes extracellular evolved gas bubbles that are then relocated to the lungs.[103]

Hypobaric Ascent Limit

The need for high-altitude bombing during WWII and the rapid advancement in jet engine development after the war put aviators at risk for DCS, hypoxia, and hypothermia until pressurized and air-conditioned aircraft cabins became common. Before these technical advances occurred, researchers in Canada and the U.S. characterized DCS, mostly with young airmen in training, using hypobaric chambers.[16,104,105] It was quickly realized that the altitude attained, time spent at altitude, and exercise at altitude increased the risk of DCS, both pain-only DCS and serious DCS linked to reactions in the cardiovascular and nervous systems.[106,107] Never again will such provocative testing be performed, and "modelers" of DCS must be content with these data to define the upper range of dose-response curves.

Denitrogenation with enriched O_2 mixtures dramatically reduced both pain-only and serious DCS, and most fit young men could tolerate a degree of depressurization even without benefit of a PB. During the war years, criteria for a successful ascent centered around having enough time to perform the mission before DCS symptoms became debilitating. Under these extreme conditions, ascents to between 6096 and 7620 m (20 000 and 25 000 ft) were acceptable in most operational settings. Several studies were initiated to identify and screen out "weak links" as a means to reduce the impact of DCS on the mission. These efforts were abandoned as ineffective and costly, but they highlighted the reality of between and within subject variability to DCS. As the interest in aviator DCS increased after WWII, primarily through the USAF and NASA, a systematic approach led to a better understanding of hypobaric ascent limit. A shift in thinking from "tolerable" symptoms to the first onset of mild symptoms also reduced the threshold altitude for DCS.

Each year millions of people on commercial flights are quickly exposed to between 1219 and 1829 m (4000 and 6000 ft) altitude for long periods. Most would agree that a rapid ascent to 3048 m (10 000 ft) does not incur a significant risk of DCS, but hypoxia soon limits useful physical activity. The use of enriched O_2 at higher altitudes confounds the basic question about the DCS limit to direct ascent on air.[108] In addition to defining the threshold of evolved gas and the interaction of the evolved gas with living tissues that produce symptoms, there are practical reasons to define a hypobaric ascent limit. Prebreathing takes time and resources, but a spacesuit that is pressurized to greater than the lowest pressure that will cause VGE and DCS could be an option to eliminate the risk of DCS.[15]

Just as divers can ascend to the surface after saturation to about 17 feet of seawater (FSW),[109] aviators can ascend to about 3962 m (13 000 ft) altitude[110] without denitrogenation. The threshold depressurization for divers and aviators has decreased since the beginning of the 20th century.[109,111,112] Initial empirical observations suggested that an ascent from 33 FSW to the surface was acceptable, and that matching the ratio of pressure change of an ascent to 5486 m (18 000 ft) altitude should be possible. Two references document about 25 FSW,[34,111] and recent work with a no PB spacesuit suggests that 4420 m (14 500 ft) altitude is close to a no-DCS ascent, with VGE still produced at an altitude of 3505 m (11 500 ft).[28] Webb et al[113] showed that a spacesuit at 9.5 psia (11 500 ft) certainly prevented DCS. So, there is some threshold below which the gas that is evolved after depressurization is insufficient to elicit symptoms, even if it is difficult to establish this without exception. Table 2, modified from Conkin et al,[28] lists hypobaric exposure pressures and the associated DCS and VGE incidence.

Kumar et al[114] and Webb et al[44] summarized the information in Table 2 and other information about altitude threshold but came to different conclusions. Kumar stressed that any threshold for symptoms is conditional on other factors, which calls into question the definition of

threshold if threshold is indeed conditional. Kumar's lowest conditional threshold was 3353 m (11 000 ft) altitude. Webb reported about 5% DCS for 6096 m (20 000 ft) altitude. Probing for the least amount of decompression dose to elicit symptoms is a difficult task since there are always exceptions to the rule.[115,116]

Table 3. Tests to Find Threshold Altitudes for DCS and VGE

$P1N_2/P2$	P2 (psia)	DCS cases/n	VGE cases/n	reference
1.49, day 1 of 3	7.8	2/64 = 3.0%	28/64 = 43%	Dixon et al,[117,118] Conkin et al[28]
1.43, day 2 of 3	7.8	2/62 = 3.0%	29/62 = 46%	Dixon et al,[117,118] Conkin et al[28]
1.42, day 3 of 3	7.8	1/60 = 1.6%	25/60 = 41%	Dixon et al,[117,118] Conkin et al[28]
1.40	8.3	1/31 = 3.2%	8/31 = 26%	Webb et al,[119] Smead et al[120]
1.36	8.5	0/9 = 0%	3/9 = 33%	USAF pilot study,* Conkin et al[28]
1.29	9.0	0/16 = 0%	7/16 = 43%	USAF pilot study,* Conkin et al[28]
1.22	9.5	0/6 = 0%	1/6 = 17%	USAF pilot study,* Conkin et al[28]
1.22	9.5	0/31 = 0%	8/31 = 26%	USAF pilot study,* Conkin et al[28]
1.22, day 1 of 5	9.5	0/23 = 0%	0/23 = 0%	Webb et a,[42,113]Dixon and Krutz,[121] Conkin et al[28]
1.11, day 2 of 5	9.5	0/22 = 0%	0/22 = 0%	Webb et al,[42,113]Dixon and Krutz,[121] Conkin et al[28]
1.10, day 3 of 5	9.5	0/22 = 0%	0/22 = 0%	Webb et al,[42,113]Dixon and Krutz,[121] Conkin et al[28]
1.10, day 4 of 5	9.5	0/22 = 0%	0/22 = 0%	Webb et al,[42,113]Dixon and Krutz,[121] Conkin et al[28]
1.10, day 5 of 5	9.5	0/22 = 0%	0/22 = 0%	Webb et al,[42,113]Dixon and Krutz,[121] Conkin et al[28]
1.16	10.0	0/8 = 0%	2/8 = 25%	USAF pilot study,* Conkin et al[28]

*USAF pilot studies using subjects with a history of DCS and VGE.

Piccard performed a seminal experiment in 1941[122] to understand ascent limits for divers and aviators. He depressurized 2 equal volumes of water, 1 of which was equilibrated at 5 ATA before a depressurization to 1 ATA and the other of which was equilibrated at 1 ATA before a depressurization to 0.2 ATA. He observed that the 5 to 1 ATA depressurization caused many small bubbles to form in the water, producing a "milky cloud." In the 1 to 0.2 ATA depressurization, a few large bubbles formed. The total evolved volume was identical after both experiments, but the time to reach the final evolved volume was shorter in the 5 to 1 ATA depressurization. Piccard extrapolated his results to 2 fictitious depressurizations, 1 in a diver and 1 in an aviator

where the ratio of P1 to P2 in both was 5, just as in his experiment. He knew that the diver would certainly die, but not the aviator.

Piccard also knew that the evolved volume at P2, expressed as N_2 volume or total gas volume, would be identical after both depressurizations (isovolume). If the volume evolved is the critical variable, the 2 depressurizations should produce equally serious outcomes (isoincidence) if an infinite time in a closed system is assumed. A closed system means that blood does not transport N_2 to or from the tissues at P2. However, in the Discussion, Piccard suggested that differences in the probability of bubble formation due to the critical radius (r_c) concept and the greater relative loss of N_2 from the tissues of the aviator than from those of the diver, because of a reduced rate of nucleation, accounted for the observed differences in outcome between the aviator and the diver. The historical concept of r_c is that a bubble radius exists that would be in mechanical equilibrium with a given depressurization where it neither grows nor shrinks: $r_c = 2\gamma/(P1 - P2)$, where γ is surface tension. Tikuisis and Gerth[64] summarize contemporary thoughts about r_c and the reality of heterogeneous nucleation. Nuclei that are present in the tissue with radii greater than r_c for a given depressurization would grow and those that have smaller radii would shrink and disappear. Surface tension, which is effective on very small bubbles, increases the bubble ppN_2 to reduce the tissue ppN_2 – bubble ppN_2 difference, thus reducing diffusion of N_2 into the bubble and slowing the initial bubble growth. Piccard's early experiment highlights the limits of the basic critical volume release hypothesis[123] by introducing the complexities of bubble nucleation rate and bubble growth rate, and the reality of evolved gas in an open system.

It has been observed that the lowest P2 to which a diver can ascend without developing DCS, be it a diver saturated at an initial pressure (P1) or a diver returning from a no saturation dive, is described by a straight line with a negative y-intercept on a plot of P2 vs. P1[110]. Extrapolation of such a line into hypobaric pressures does not result in safe depressurizations, indicating that extrapolation of the safe diver line to altitude is invalid. Over the pressure range spanned by human hypobaric exposures and hyperbaric air exposures, the best separation between no DCS and DCS on a P2 vs. $P1N_2$ plot seems to be a curve that approximates a straight line in the hyperbaric region but bends toward a negative x-intercept. A consequence of isoprobability isopleths that intercept on the negative $P1N_2$ axis of a P2 vs. $P1N_2$ plot is that constant P(DCS) is described by TRs that decrease as P2 decreases. The negative x-intercept for all isoprobability isopleths is likely a consequence of: (1) the combined contributions of the limiting boundaries of the decompression test envelope due to hypoxia, (2) an artifact established by the $P1N_2$ calculation since the horizontal position of a test result on a P2 vs. $P1N_2$ plot is obtained using a 360-min half-time compartment, (3) the influence of exercise at altitude on the genesis and growth of bubbles, and (4) the contribution of metabolic gases and the O_2 window[62] to hypobaric DCS, which can only be inferred from a P2 vs. $P1N_2$ plot. Isopleths that have a negative x-intercept all cross a unique positive P2 when $P1N_2$ is 0, indicating the reality of ebullism at very low pressure as dissolved metabolic gases and water vapor come out of solution. Figure 4 shows 3 isoprobability isopleths derived from Conkin et al.[67]

The isopleths in Figure 4 might represent isovolume isopleths that are defined by considering the summed volume from a subpopulation of critical radii nuclei activated to grow depending on initial and final pressures; they are expressed as the volume at the final pressure. One possibility that accords with physics is that depressurization from hyperbaric exposures along an isoprobability (isovolume) line produces many small bubbles after ascent from deep dives, fewer larger bubbles after ascent from shallower dives, and finally larger and fewer large bubbles on hypobaric depressurizations. The critical volume for the 0 isoprobability isopleth is

the same along only 1 particular isovolume isopleth, the curve that defines the hypobaric ascent limit.

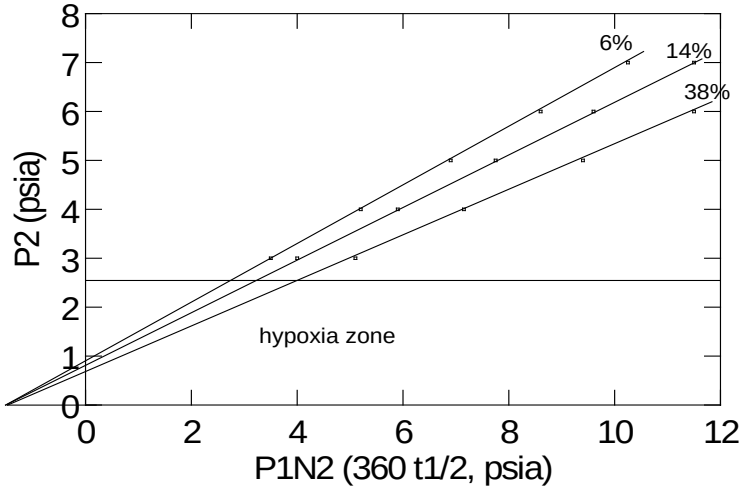

Figure 4. Three isoprobability DCS isopleths for hypobaric exposures converging on the negative x-intercept instead of the negative y-intercept, where extrapolated diver isoprobability isopleths converge.

As described above, given 2 exposures with the same TR, the P(DCS) is greater for the case in which ambient pressure is lower.[67,69,124] Consider 2 depressurizations. In the first, $P1N_2$ is 5.0 psia in the tissue before an ascent to 3.75 psia, and the TR is 1.33. In the second, $P1N_2$ is 5.7 psia in the tissue before an ascent to 4.30 psia, and the TR is also 1.33. All else being equal, we might expect the P(DCS) to be the same. In a physical system and given infinite time, the total evolved gas in the 2 examples above would be identical.[122] However, TR is not closely related to bubble size since the presence of metabolic gases will cause bubbles to grow larger at lower ambient pressure.[125] This is seen in an equation by Van Liew and Burkard[126] that relates the total volume of evolved gas expressed at ambient pressure to TR:

$$\Delta V(a)tot = \alpha N_2 * Vtis * Ps * [(TR / FN_2) - 1\ ], \quad (4)$$

where $\Delta V(a)tot$ is the total volume (ml) of evolved gas in bubbles, expressed at ambient pressure; αN_2 is solubility of N_2 in tissue; Vtis is the volume (ml) of tissue available to bubbles; Ps is standard pressure; TR is the ratio of tissue N_2 pressure to ambient pressure ($P1N_2/P2$); and FN_2 is the fraction of N_2 in a bubble. As the total pressure decreases, the FN_2 in a bubble must also decrease due to the presence of a constant metabolic gas pressure in the bubble. Notice that as FN_2 decreases as ambient pressure decreases, the total evolved volume increases given the same TR. In the above case with a constant TR of 1.33 but 2 different ambient pressures, the total evolved volume is about 1.8 times larger at 3.75 psia than at 4.3 psia.

Astronauts will continue to perform EVAs in the Orlan suit when needed and cosmonauts will continue to perform EVAs in the EMU when needed. Other ISS partners will do EVAs in

either suit. The operational philosophy is that astronauts/cosmonauts will follow the PB procedures developed for each suit. The rationale is that testing on Earth and operational experience in μG has validated each PB procedure. Different acceptable R-values, 1.65 for the EMU from the shuttle and 1.85 for the Orlan, are possible for approximately equivalent risk since suit pressures are different.

Diving Astronauts

Our focus in previous sections was on preventing DCS during EVAs, but an EVA is just the culmination of many hours of training under both hyperbaric and hypobaric conditions. Policies and procedures are followed that minimize the P(DCS) after hyperbaric suited exposures in the U.S. Neutral Buoyancy Laboratory (NBL) and the Russian Hydrolab, during suited exposures in hypobaric chambers, and after diving activities from the NASA Extreme Environment Mission Operations (NEEMO) underwater habitat. Objectives of an EVA are choreographed on flight-like hardware submerged in 40 feet of fresh water (FFW) at the NBL. Training emulates actual EVA scenarios and can last for 6 hr. To avoid DCS after long exposures to a maximum physiological depth of 50 FFW (pool depth plus suit pressure) astronauts breathe nitrox, a mixture of 46% O_2 and 54% N_2. At this extreme, the equivalent air depth is 23 FFW. Breathing nitrox eliminates the need for staged depressurization at the end of a long training session, and some details about diving practices are available from Fitzpatrick and Conkin.[127] Astronauts also train and maintain proficiency in operating the spacesuit by exposure to vacuum in various altitude chambers at JSC. In some cases, astronauts are required to fly in the T-38 aircraft or on commercial airlines shortly after a hyperbaric or hypobaric exposure. Specific directives, based on best available research,[128-130§] dictate the proper surface intervals and PB procedures that minimize the P(DCS) on a subsequent hypobaric exposure. Procedures and equipment are available to treat DCS on orbit and after training activities, and a disposition policy returns astronauts to flight status after undergoing a successful treatment regime. Adherence to these policies and procedures, which undergo periodic review and update, minimizes the chance that DCS will become a medical concern to the astronaut or hinder the completion of training or safe execution of an EVA.

Decompression Sickness and Venous Gas Emboli from Validation Trials

Validation testing often precedes implementation of a PB protocol for space operations. The inefficiency of an in-suit PB and possibility of a break in PB during transition from an O_2 mask to the spacesuit required that NASA validate the staged 10.2-psia protocol in the early 1980s. Variations of similar protocols soon emerged, along with a desire to summarize all of the results with a simple decompression dose. In addition to the DCS outcomes, routine ultrasound bubble monitoring provided an unbiased assessment of decompression dose. Spencer's 0 – IV categorical scale[131,132] was adopted, and the following standard 4-min evaluation scheme to improve bubble detection and grading was implemented at JSC:[133] A Doppler technician relocated and optimized an acceptable Doppler ultrasound blood flow signal in the pulmonary artery from a sitting or semi-recumbent subject in an altitude chamber in about 15 sec. The subject was then instructed to rhythmically flex each limb about 3 times in sequence, moving all joints in the limb. The movement dislodged small bubbles sequestered in venous capillaries, and the grade of VGE passing beneath a 5.0- or 2.5-mHz ultrasound wave was assigned by an investigator outside the altitude chamber.

§*Reference 130 is our Test 10.*

Figure 5 illustrates decompression dose-response curves for DCS and VGE outcomes from 341 exposures to 4.3 psia in altitude chambers at JSC. Subjects breathed 100% O_2 through a mask, and were otherwise in a comfortable shirtsleeve environment. The mean exposure time was 4.4 ± 1.3 hr SD, and subjects ambulated from 1 exercise station to another. Exercise included cranking and pulling against modest resistance, and torquing fixtures to simulate the type and intensity of work performed during a contingency EVA; details are in Conkin et al.[9] At intervals of about15 min, the pulmonary artery was insonated with a bubble detector in recumbent subjects. Given enough exposures over a range of decompression doses, a predictive equation for DCS and VGE was created, in this case from the Hill equation. The wide 95% confidence limits for DCS and VGE suggest that factors other than simple decompression dose influence the outcome. There is more to accepting a denitrogenation protocol than just the raw incidence of DCS or VGE. The nature of the symptoms, how the incidence of DCS is related to the intensity of the symptoms,[134] and their response to re-pressurization[7] are as important as the overall incidence of DCS and VGE to a final decision to accept a protocol.

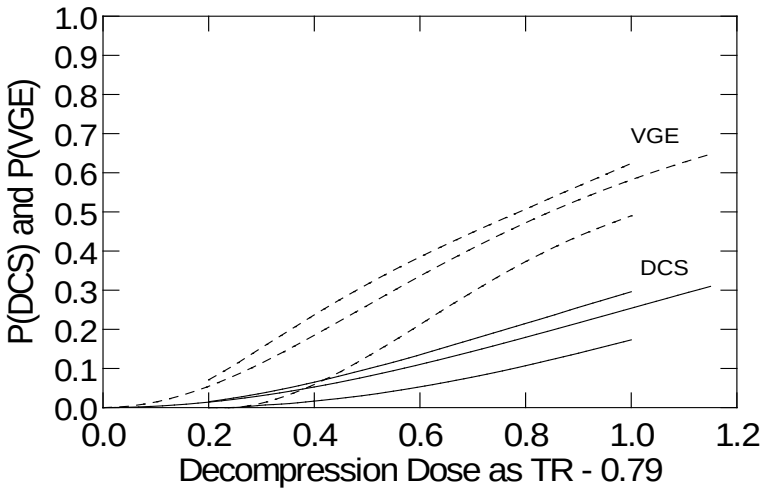

Figure 5. P(DCS) and P(VGE) increase as decompression dose increases. The 95% confidence limits (shorter curves) above and below the best estimate help to visualize uncertainty in the outcome.

Table 2** summarizes DCS and VGE results archived at JSC in the NASA Hypobaric Decompression Sickness Database. Tests done for NASA by Brooks AFB are not shown here, but are available in the Air Force Research Laboratory Altitude Decompression Sickness Research Database archived at Wright-Patterson AFB. Operational questions dictated the sequence of testing in Table 2. The first trials evaluated the 3.5- (Tests 1a and 2a) and then the 4- hr in-suit PBs (Tests 3a and 3c), and the subjects in these protocols often "crossed over" to validate the 10.2-psia staged PBs. Several variations of the staged protocol tested the benefit of an initial 60-min PB before ascent to 10.2 psia, different durations at 10.2 psia, and different final in-suit PB

**The table, first shown on page 8 of this document, is repeated on the following page to ensure ease of access.

times before depressurization to 4.3 psia (Tests 1b, 1c, 1d, 2b, 3b, 3d). Repetitive exposures to 4.3 psia while living at 10.2 psia addressed issues of fatigue and cumulative DCS and VGE risk (Tests 4a through 4f). Cumulative risk was not found to be a concern in repetitive hypobaric depressurizations,[28,135,136] so repetitive EVAs from the shuttle were deemed safe. Women were first used at JSC in a trial of a 6-hr PB (Test 5a) and during a novel 10.2-psia staged protocol in which simulated suit pressure was 6.0 psia with 60% O_2. A trial of an 8-hr resting PB (Test 5b) established the benefits of extreme prebreathing, even if extreme prebreathing is not practical from an operational perspective. The influence of high work rate during EVA was evaluated using a row machine,[21] a consequence of which being 2 cases classified as serious DCS in subjects from Test 7a. Exercise intended to counteract deconditioning in space did not influence the subsequent DCS and VGE outcome given that the interval between the exercise and simulated EVA was 16 hr (Tests 8a and 8b, Kumar et al[137]). The consequences of ambulation before and during an altitude exposure were evaluated at both 6.5 and 4.3 psia in the Argo series, starting with Test 9a and ending with Test 11a. Test 9a included ambulatory controls and Test 9b included the same subjects but at 6-degree head-down bed rest for 3 days before and during the 3-hr exposure to 6.5 psia without prior PB. The incidence of Grade III plus IV VGE was less in the bed-rest group and it took longer before Grade III and IV VGE were first detected.[138] Astronauts sometimes fly in commercial airliners or the T-38 jet shortly after training in the NBL. Test 10 included a hyperbaric and then a hypobaric exposure to evaluate the consequences of flying after diving under our specific training conditions.

Table 2. Summary of DCS and VGE in Tests from 1982 – 2009

Test	P2 (psia)	conditions	number m	number f	mean age	DCS	VGE (any Grade)	VGE (Grade IV)
1a	4.3	P	11	0	34.5	4	7	4
1b	4.3	S	13	0	32.3	3	11	7
1c	4.3	S	12	0	32.0	4	7	6
1d	4.3	S	3	0	39.6	2	3	2
2a	4.3	P	23	0	31.6	7	15	8
2b	4.3	S	22	0	31.5	6*	10	7
3a	4.3	P	28	0	31.0	6	13	11
3b	4.3	P,S	35	0	30.1	8	20	8
3c	4.3	P	14	0	32.5	3	5	1
3d	4.3	P,S	12	0	28.5	2	5	2
4a	4.3	P,S	12	0	30.1	1	7	3
4b	4.3	P,S	12	0	30.1	0	2	1
4c	4.3	P,S	12	0	30.1	0	4	1
4d	4.3	P,S	12	0	30.1	0	0	0
4e	4.3	P,S	12	0	30.1	0	4	1
4f	4.3	P,S	12	0	30.1	0	0	0
5a	4.3	P	19	19	31.5	4	11	4
5b	4.3	P	11	0	32.0	0	0	0
6	6.0	S	15	14	32.9	1	3	0
7a	6.5	direct ascent	11	0	28.2	4†	8	6
7b	6.5	direct ascent	11	0	28.2	2	8	4
8a	6.5	direct ascent	29	11	32.5	7	20	13
8b	6.5	direct ascent	30	11	32.6	10*	22	17
9a	6.5	direct ascent	15	9	32.1	1	12	7

Test	P2 (psia)	conditions	number m	number f	mean age	DCS	VGE (any Grade)	VGE (Grade IV)
9b	6.5	A	14	9	33.8	2*	6	1
9c	4.3	A	9	2	34.8	3	5	4
9d	4.3	A	6	1	36.4	0	2	0
9e	4.3	E,A	7	0	34.6	0	2	0
10	10.1	FAD	14	5	31.7	1	6	3
11a	4.3	P,A	16	12	33.2	3	9	4
11b	6.5	direct ascent	1	3	39.5	0	1	0
Phase I	4.3	P,E,S,A	33	14	29.1	9	23	2
Phase II	4.3	P,E,S,A	35	10	31.7	0	14	3
Phase IV	4.3	P,E,S,A	44	12	30.1	8	23	7
Phase V-1	4.3	P,E,A	7	2	31.5	3	5	2
Phase V-2	4.3	P,E,A	1	2	39.2	1*	3	2
Phase V-3	4.3	P,E,A	38	10	36.9	7	25	5
Phase V-4	4.3	P,E,A	3	3	31.5	3	3	1
Phase V-5	4.3	P,E,S,A	37	11	32.3	2	14	8

Conditions: P, some PB occurred before ascent; S, a portion of the PB was spent at 10.2 psia breathing 26.5% O_2; A, subjects were "adynamic" (no ambulation before or during the altitude exposure); E, a prescribed exercise was performed during some interval of the PB; and FAD, flying after diving.
*One case was classified as Type II DCS; †2 cases were classified as Type II DCS.

As part of the NASA Prebreathe Reduction Program, recent trials evaluated the benefits of different exercise regimens during PB: short and intense, long and mild, and combinations of the two. The goal was to combine known factors that reduce the P(DCS), such as exercise and adynamia, with representative EVA work simulation in a PB for ISS construction and maintenance. Avoiding ambulation during PB and at altitude does reduce the incidence of DCS and VGE in the lower body, so adynamia is included in all current validation testing as an analog to working in μg,[88,89,95] although there are contrary observations.[139] Researchers evaluated the influence of combined intense dual-cycle ergometry in Phases I through IV for 10 min with additional low-intensity exercise on the DCS and VGE outcome. After completing the initial 50 min of PB at site pressure, subjects were depressurized to 10.2 psia over 30 min while still breathing 100% O_2, and then 30 min were spent at 10.2 psia breathing 26.5% O_2 to reproduce suit-donning conditions in the ISS airlock. Then 100% O_2 was reintroduced into the subjects' masks and they were re-pressurized to site pressure within 5 min to complete the final 35 min of PB. After a 150-min total PB time, a final depressurization from site pressure to 4.3 psia was completed in 30 min, and subjects simulated EVA work tasks at 4.3 psia for 4 hr. Phase II met the accept conditions, as described earlier, for an ISS PB and became the operational Exercise PB protocol. In trials from Phases V-1 to V-4, researchers evaluated whether mild exercise that could be performed during an in-suit PB at 14.7 psia would be effective, but no form of mild exercise met the pro-spective accept conditions. The final trials in this series (Phase V-5) extended mild exercise and the total PB time to 190 min, including a 30-min suit-donning step at 10.2 psia that became the operational ISLE PB protocol. Instead of referencing publications over a period of 30 years that cover the specifics of all trials, the reader can find details in Conkin et al[9,50] for trials from 1a to Phase IV. Details from Phases V-1 to V-5 are in Gernhardt and Pollock.[140] Phase I through V-5 trials could not have been performed quickly and safely without the assistance of dedicated in-vestigators at Duke University, Hermann Hospital, the University of Texas, and the Defense Research and Development facilities in Toronto.

Age, Gender, Aerobic Fitness, Hydration, and Patent Foramen Ovale

Weathersby,[141] Kumar et al,[137] and Webb et al[142] have observed that some divers and aviators are particularly resistant or susceptible to DCS and VGE. Depressurization schedules developed to protect the most susceptible are then ultra-safe for the resistant, and therefore are not very efficient. There thus is a long history of persistent efforts to identify those who are susceptible, and to identify the physiological and anatomical factors associated, as either a cause or a correlate, with susceptibility.[134] Selection schemes, except for natural selection, have not developed past the conceptual stage primarily because prospective, well-controlled studies with adequate sample size are expensive.

A cursory listing of recent publications is provided for divers and aviators concerning the association of age;[9,109,112,143,144] gender;[129,145-147] aerobic fitness;[148-150] hydration;[151] patent foramen ovale (PFO);[152,153] and exercise before, during, and after depressurization[97,102,103,154] with DCS and VGE. One challenge in understanding the contribution of these factors to DCS and VGE outcomes is that all are a part of the whole, and it is difficult to isolate the contribution of 1 factor. In reality, DCS and VGE outcomes are multifactorial and confounded by many factors, particularly the decompression dose.[155]

A practical approach, given a large sample of quality research results, is to perform a multivariate statistical analysis in which the uniqueness of each trial becomes part of the reason, along with other explanatory variables, for the outcome. In other words, a multivariate analysis, such as logistic regression or survival analysis, identifies and controls for confounding and interacting variables so that a better interpretation of the outcome is possible.[68,70] Thus, multivariate analysis with large numbers of quality research data with an appropriate range of explanatory variables is necessary to assign the appropriate contribution to an explanatory variable. This approach has not been generally used, as it contributes to contradiction and confusion in the literature.

Relationship between Venous Gas Emboli and Hypobaric Decompression Sickness

Ever since silent bubbles were first associated with modest hyperbaric and hypobaric exposures, there has been a vigorous debate about the value of VGE detected in the pulmonary artery or other veins to predict subsequent DCS outcome.[156] The fact that bubbles are present without overt symptoms suggests that, at best, the presence of VGE is a necessary but not sufficient condition for DCS, and relationships between the 2 are correlative as opposed to cause-and-effect. Correlative relationships differ from 1 study to the next depending on many factors, such as the decompression dose, the type of breathing gas,[108,157] the type of ultrasound equipment, the training of the Doppler technician, and the methods used to quantify the Doppler signals, such as simple bubble grades or more sophisticated "time-intensity" approaches.[158] However, the absence of VGE is strongly associated with the absence of DCS.

The positive and negative predictive values of VGE have been explored in both divers and aviators.[69,138,156,159] The desire to have a single global understanding about the relationship between VGE and DCS is frustrated because of differences in bubbles between divers and aviators, and even differences attributed to gender.[146] Trials that produce Grade IV VGE in 50% of divers will never be sanctioned since this would result in an unacceptably high incidence of DCS, as well as a high incidence of serious DCS. Grade IV VGE are routinely assigned in hypobaric depressurizations, however, even after conservative PBs.[45] DCS incidence on the order of 20% is

common, with only about 1% of all exposures resulting in serious DCS in NASA testing and a higher percentage in tests of protocols for the USAF.[5] Divers returning to 1 ATA from a provocative SCUBA dive may produce many small bubbles, predominately composed of N_2. In contrast, aviators may produce fewer large bubbles composed of as much as 70% metabolic gases.[125,126,160] Since the gas composition of VGE in divers and aviators differs, it is reasonable to expect that the association between VGE and DCS reflects this difference. In summary, a global understanding about the relationship between VGE and DCS is not yet available, the absence of which results in contradictions when the experiences of divers and aviators are compared.

It is more than coincidental that VGE are often detected in high intensity, coming from a region of the body in which a sign or a symptom may appear. Table 4 shows that the positive predictive value for DCS of any VGE grade or of Grade III and IV is only 32% or 39%.[161] Someone with prior knowledge of even Grade IV VGE from a particular limb in an aviator is less than 40% confident that a DCS symptom will follow. The absence of VGE has a negative predictive value of 98% in these data, but much less in other hypobaric data.[162,163] So, it is more informative to know that an aviator or astronaut has no VGE in the pulmonary artery if the goal is to predict a subsequent DCS outcome.[164]

Table 4. Measures of Association between VGE and DCS

measure	Grades 0 – IV (n = 1322)	Grades 0, III, IV (n = 1210)
sensitivity	0.922	0.917
specificity	0.718	0.787
+ predictive value	0.323	0.391
- predictive value	0.980	0.980

Although a 1-to-1 cause-and-effect relationship between VGE and DCS does not exist, there is a consistent temporal association between VGE and DCS. Figure 6 shows this temporal pattern. Not everyone who has VGE has subsequent DCS, and a few who do not have VGE do have DCS. The caveat here is that a similar VGE onset-and-recovery pattern is present in those who do and those who do not develop DCS. Any association between VGE detected in the pulmonary artery and pain-only DCS in a distant limb is subtle.

There are 78 subjects that have DCS onset times associated with 78 VGE onset times, with a mean TR of 1.67 ± 0.15 SD, in the NASA historical database. The mean DCS onset time was 120 ± 71 min SD and the mean VGE onset time was 72 ± 55. In 150 other exposures, VGE were not associated with a report of DCS. The 150 exposures with VGE but without DCS had a mean VGE onset time of 90 ± 65 min and a mean TR of 1.65 ± 0.19. The mean VGE onset time for all 228 exposures with VGE was 84 ± 62 min. Only 4 subjects had DCS without VGE being detected. The majority of exposures, a total of 317, had no DCS or VGE, since the goal was to validate only safe PB protocols. The same pattern held for exercise during PB, but the incidence of DCS given that VGE were present decreased slightly from 14% to 11%. It was likely, but not certain, that an individual would report a DCS symptom after VGE were detected if that VGE were detected early in the altitude exposure, if the intensity or grade of VGE from a limb region increased rapidly, and if the intensity or grade of VGE remained high.[69,161]

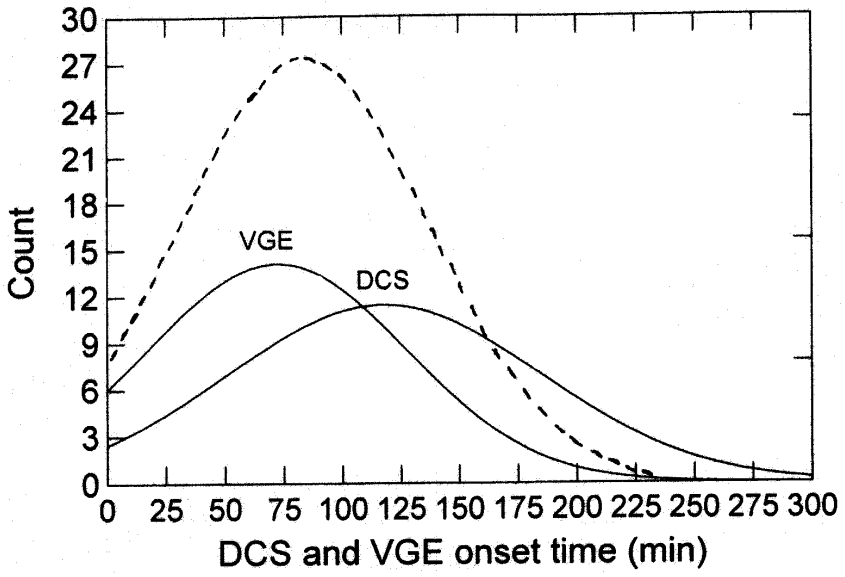

Figure 6. Time of VGE and DCS onset in 78 exposures with both present (solid curve) and in 150 exposures with VGE only present (dashed curve). The curves, all of which are skewed to the right, are the best-imposed normal distributions on histograms.

It is appropriate here to speculate on why VGE that are detected in the pulmonary artery seem disconnected from the DCS outcome even when the VGE seem to originate from a limb region. VGE moving in the venous blood and detected at a common location for all cardiac output are far removed from the site of bubble formation, so there is no guarantee that other tissues, such as fat and skin, do not contribute VGE to the venous return. There is no a priori reason why VGE cannot be produced in a limb region even if the critical volume of evolved gas needed to evoke a symptom has not been reached. Excess dissolved N_2 in muscles, tendons, ligaments, joints, cartilage, and other tissues can form bubbles in these tissues and can also diffuse into the low-pressure venous return where bubbles grow from micronuclei clinging to vascular endothelium. They accumulate, grow, and then pinch off and coalesce, to be carried with the venous return as muscle contractions "milk" the blood and bubbles into the venous return. So, it is understandable that VGE detected in the pulmonary artery are only indirectly linked to DCS symptoms. But, even a weak association is helpful to visualize the primary cause of a symptom at a distant location and the transport of excess N_2 as bubbles. Advances in ultrasound technology will soon replace speculation with clear visual evidence of stationary bubbles growing within tissues and on the vascular endothelium.

Most people prefer not to have circulating VGE, with or without a PFO. Blood is a complex fluid and, as the blood-endothelial interface forms a complex homeostatic surface, the presence of bubbles in blood and at the blood-endothelial interface could be problematic. Aviators and astronauts share 1 feature with divers: healthy lungs that provide an efficient filter for VGE.[165] Aviators and astronauts are not immune from the consequences of embolic overload, however, even in healthy lungs. Many factors in the aerospace environment compromise healthy lung function. These factors, when combined with too many bubbles entering the pulmonary circulation, can put this group at high risk.[139]

Mathematical Modeling

Statistical descriptions of DCS and VGE outcomes from hypobaric exposures using logistic regression and survival analysis as well as biophysical modeling of tissue bubble dynamics have made significant advances in the last 20 years. The integration of both approaches has produced sophisticated probabilistic models, which are briefly summarized here. Probabilistic modeling requires 4 items: (1) a data set that contains a dichotomous response variable, ie, the presence or absence of DCS, and 1 or more explanatory variables; (2) an expression of decompression dose in terms of explanatory variables; (3) a function, such as the logistic function or Hill equation, that structures the dose model so the outcome is a calculated P(DCS); and (4) a parameter-estimation routine on a computer that uses maximum likelihood.

Simple descriptions of decompression dose such as TR or ΔP approximate the true dose[68,74] while models concerning tissue bubble dynamics strive to define true dose through diffusion-based physics and consideration of mass-balance[65,166-172] Those referenced, and many others as well,[173-176] contribute to a single evolving model to describe the P(DCS) in both diving and altitude depressurizations by invoking multiple tissue compartments, multiple finitely diffusible gases, and a distribution of bubble nuclei that begins to grow at different times during depressurization. Others have also concentrated just on hypobaric depressurizations.[††] Recent advances in probabilistic modeling came through the use of techniques from survival analysis. Weathersby and Gerth[180] and Tikuisis and Gerth[64] provide additional details about probabilistic DCS modeling.

One reasonable expectation from modeling is that fewer trials, or even no trials, are performed before accepting a variation of a tested protocol if the model computes an acceptable P(DCS), P(Serious DCS), or even P(Grade IV VGE). Such was the case in a recent decision to accept the campout PB for ISS without direct testing of this variant of the shuttle 10.2-psia staged PB. Aside from increasing computational efficiency for complex models, probabilistic modeling will significantly advance when the link is quantified between evolved gas in tissue and the perception of pain by the central nervous system.[69] An assumption in modeling is that the outcome variable is known with certainty, which is certainly not the case,[12,181,182] and adds a further level of uncertainty to probabilistic modeling.

Operational and Research Experience with Decompression Sickness

Astronauts and cosmonauts working in spacesuits pressurized to between 3.7 and 5.8 psia have not reported DCS during EVAs. In contrast, U.S. and Russian research subjects who evaluate operational PB protocols in altitude chambers report about 20% DCS.[9] How do we reconcile these disparate observations? Technicians have reported pain-only DCS at JSC during suit development, and at least 1 astronaut recollected pain in a knee on 2 occasions after depressurization to 5.0 psia in the spacecraft. So, DCS is possible both in space and in a spacesuit at 1*g*. Foster and Butler[183] discussed several factors related to working in a hypobaric and μg environment that may reduce the P(DCS) in EVA astronauts.

A research setting designed specifically to monitor for DCS certainly differs from an operational setting in which other tasks are the focus of the EVA. Subjects wearing an O_2 mask who are otherwise comfortable in a shirtsleeve environment at 1*g* are not the same as astronauts who are surrounded by 100% O_2 and maneuvering in μg in restrictive and uncomfortable spacesuits. The Russians hypothesize that limited motion in the Orlan and, by extrapolation, the

[††]*References 67, 70, 137, 147, 177-179.*

EMU will be a significant factor in reducing the likelihood of DCS during an EVA. Real differences, both physiological and behavioral, thus exist that may explain the difference between research and EVA results. A bias to not report mild discomfort in an operational setting is expected. This is routinely observed in pilot training where qualification to fly is compromised if DCS is reported during hypobaric training activities. The U-2 experience, described by Bendrick et al,[184] provides an example of the difference between operational and research reports of DCS. Seventy-five percent of respondents to a questionnaire said they had DCS symptoms at least once during their careers flying U-2 aircraft, but rarely reported their symptoms to the flight surgeon.[185] Webb et al[43] reported an incidence of 77% DCS in subjects testing the 60-min U-2 PB protocol, which included mild exercise while at a simulated aircraft cabin pressure of 4.37 psia. Intense, short-duration exercise during this PB reduced the incidence to 42% in subjects, and is offered to U-2 pilots who feel the need for additional DCS protection.[47] For various reasons, astronauts and pilots are not motivated to report every small discomfort.[10] It is likely that the first report of DCS during an EVA will be a serious case of DCS.[106]

There are valid reasons why mild symptoms of DCS might be masked during an EVA. For example, many astronauts take aspirin before an EVA, so mild aches and pains are managed in advance. The EMU is a source of aches and pains of the same intensity as pain-only DCS since operational PB procedures are conservative, so many mild cases that are not reported during EVA could be attributed to pain caused by working in the EMU. Mild symptoms quickly clear during re-pressurization, so astronauts would have little incentive to report a symptom that is no longer present after the EVA. The incidence of DCS symptoms that would interfere with performance in an EMU is less than 5% in validation testing in altitude chambers.[26,28] About 85% of those reporting symptoms showed improvement in the symptom or showed no change in symptom intensity when tests were allowed to proceed past the point of the first symptom report. Since PB protocols before EVA reduce the incidence and intensity of symptoms, it is understandable that any resulting mild symptoms are unremarkable in an operational setting.

In addition to understanding behavioral bias and the masking of symptoms, we also need to understand whether the primary risk mitigation strategy of prebreathing is more or less affected by adaptations to μ*g*. All astronauts undergo readaptation in μ*g*.[186] About 2 liters of fluid from the lower extremities is redistributed into the chest and head, with a resulting decrease in total body water. Upper body venous engorgement at the expense of a reduced lower body venous capacitance does not abate even after months in space, even with a net decrease in plasma volume. As a result, denitrogenation in μ*g* may be more efficient than on Earth if a supine body position is a reasonable analog for μ*g*.[187] Lesser interventions than adaptation to μ*g* are known to modify N_2 washout.[188,189]

Jones et al[190] did the early work to understand the effects of blood perfusion on N_2 uptake and elimination in tissues. Behnke et al[39,191,192] showed how body composition and exercise during PB influenced N_2 removal. Studies by Balldin[187,193] and Balldin et al[194,195] showed how increased ambient temperature, supine body position, and immersion in water increased N_2 removal from adipose and muscle tissue as well as from the entire body. Theis et al[196] confirmed and supplemented these data by examining whole-body N_2 washout during supine body position. Balldin and Borgstrom[197] and Curry & Lundgren[198] reported that even negative-pressure breathing accelerates N_2 washout. The most recent efforts to understand N_2 removal under various experimental conditions, including μ*g* simulation, were undertaken by Vann and Gerth[199] and Gerth et al.[200,201] Various experimental interventions resulted in a wide range of tissue N_2 washout, from about 8 ml/kg for seated subjects to about 24 ml/kg for subjects who performed 50 W of continuous

arm and leg exercise for 2 hr while in a 6-degree head-down tilt during a 3-hr PB. It is therefore reasonable to hypothesize that the altered physiology and anatomy in response to μ*g* adaptation modifies the amount of N_2 removed from the body during PB.[88,95,202]

It is also possible that DCS has not actually occurred during EVA.[81,203] Astronauts perform more prebreathing than is tested on the ground, since ground-based PBs are translated into Aeromedical Flight Rules, and more than the minimum protection is always provided. TR computed for the first 142 staged PB protocols from the shuttle was 1.51 ± 0.07 SD compared to 1.52 ± 0.26 for 245 research subjects at JSC with 18% DCS, who were ambulatory during testing. Ambulation encourages DCS and VGE from the lower body, so the absence of ambulation in μ*g* likely reduces the incidence of DCS below 18% during EVA. TR also decreases during subsequent EVAs, from 1.51 to 1.48 for the second EVA. This is because breathing 100% O_2 during a 6-hr EVA continues the denitrogenation over multiple EVAs during a shuttle mission, and because the crew lives at 10.2 psia, where tissues eventually equilibrate to a ppN_2 of about 7.5 psia. Waligora and Pepper[204] and Waligora and Kumar[205] summarized physiological aspects of working in space during the first 59 shuttle person-EVAs.

The astronaut is surrounded by 100% O_2 for some of an operational PB and all of the EVAs. It is unclear how much N_2 is transferred out of the body through the skin of astronauts, or into the body of subjects surrounded by air in altitude chambers. However, any benefit would go to the astronaut.[206] Warm ambient temperature enhances denitrogenation.[187] Astronauts in the shuttle and performing EVA often report they are cool to cold. It is likely that research subjects are in a more comfortable thermal environment during a PB and EVA simulation than are astronauts. It is unclear how skin temperature that is cool due to the liquid cooling and ventilation garment affects the transport of N_2 across the skin during the in-suit portion of the PB and the EVA. Knowing anything conclusive about N_2 washout in space or the unbiased information from an in-suit Doppler bubble detector would greatly help us to understand the true risk of DCS in EVA astronauts.[161,207-209]

Astronauts are physically active during PB, and exercise during PB accelerates N_2 washout.[43,51] Subjects in early trials at JSC were inactive during their PB. Aerobic fitness, as measured by VO_2 peak, is not, per se, associated with resistance to pain-only DCS. An analysis of VO_2 peaks in subjects failed to show a strong association with DCS in exposures without PB and with resting PB. However, the association was strong when exercise was included as part of the PB.[210,211] The benefit of exceptional aerobic fitness toward reducing P(DCS) is only realized when exercise is exploited as part of the PB. A person with low VO_2 peak can reduce his or her P(DCS) to match that of a fit person by increasing the intensity of exercise in the same PB time, by increasing the length of the PB, or by some combination of both.[50,210] Cumulative O_2 consumption during PB is not the only consideration to reduce the P(DCS). Effective N_2 elimination seems to depend on how the exercise is performed more so than just total O_2 consumption per unit time normalized to body mass. There are also constraints as to the type and duration of exercise that is prescribed during the PB since a long EVA awaits the astronaut after the PB. Women research subjects did not benefit to the same degree as men research subjects when exercise during PB was prescribed as $\%VO_2$ peak.[212] Astronauts as a group are more physically fit than their age-matched research subject counterparts. Current astronauts are about 10 years older than research subjects, but have similar aerobic fitness as measured by VO_2 peak. Therefore, subjects as old as astronauts would be less fit. If fitness is linked to DCS susceptibility,[142,144,150,213-215] astronauts as a group, under any PB condition, may be less susceptible to DCS than subjects of comparable age.[9] Finally, the "effective" exercise in the EMU might be less than or different from the exercise

on Earth that is used to simulate EVA activity, and exercise is certainly an important consideration for DCS risk at altitude.

In-suit Doppler Effort

Monitoring for venous bubbles in the pulmonary artery as the entire right-heart cardiac output enters the pulmonary circulation is the simplest approach to take in performing an unbiased assessment of the effective decompression dose, even if VGE are not directly linked to subsequent DCS. Noninvasive Doppler ultrasound bubble detection technology quickly advanced in the mid-1970s to the point at which small, battery-operated devices were safe to use in operational settings. Investigators at Brooks AFB in the early 198's proposed that a 5-mHz continuous wave bubble detector with simple analog recording be interfaced with the U-2 aircraft pressure garment. But, scientific rationale and engineering capability were not enough to implement this system, even as a research tool. Because the idea was valid and the rewards were great, efforts persisted at JSC to provide an automated venous blood bubble monitor for use in the EMU. Several prototypes were developed and tested at JSC. A parallel effort was also initiated by the Russians, who eventually monitored subjects who were wearing the Orlan suit during altitude chamber flights.

The ability to acquire a stable, quality blood flow signal was verified during brief periods of μ*g* during parabolic flight. The viscera within the chest stabilized in μ*g*, which allowed for good signal quality even under modest body motion.[216] Technical advances continued, especially in the design of the probe. The final configuration was a triangular flat probe head with 1 transmit and 3 receive sensors spaced so that a rib was always spanned regardless of probe orientation on the chest over the pulmonary artery. The sensor had to perform in a “hands-off” operation once the EMU was donned. Various taping and strapping options were evaluated to maintain orientation of the probe. Techniques to maintain ultrasound coupling between the sensor and skin were needed since hours of use in a hypobaric environment would evaporate the ultrasound gel. Issues of suit fit with the Doppler device inside the EMU were evaluated during normal training activities at the NBL. A final design emerged where the battery module, 2.4-mHz continuous wave ultrasound electronic module, and digital recorder module were separate on a belt worn around the waist. The system was flown on STS-87 and worn by Winston Scott while in the shuttle, not in the EMU. The system was evaluated at 6.5 psia on 4 subjects in an altitude chamber (Test 11b), and recorded VGE in 1 subject. Finally, the system was used in the underwater habitat *Aquarius* where astronauts on the NEEMO 5 mission wore the unit for several hours after returning from dives deeper than the 56-FSW saturation depth of the habitat. A significant finding was the recording of false positive VGE signals. Gas entrained by swallowing liquids was detected due to the proximity of the sensor to the esophagus.[217,218] This was significant since the astronauts are encouraged to drink water from a 32-oz drink bag within the EMU during long EVAs. The Doppler device, training on the device, and use of the device under real-world conditions was successful.

A final operational system did not materialize in spite of a successful research and development program for an automated in-suit bubble detector. Safety concerns about the battery-operated device within the 100% O_2 EMU environment halted the effort, and also prevented exposure of an astronaut to 4.3 psia while in shirtsleeve in the shuttle or ISS airlock as a means to evaluate the device. There was also an understandable resistance to implement this system out of concerns that the results could impact future EVA assignments. There was a related biomedical spin-off effort to develop an ambulatory stroke monitoring system, much like the

ECG [electrocardiogram] Holter monitor system used to record abnormal ECG patterns in cardiac patients. Paradoxical stroke is not well understood, and a system that insonated the midcerebral artery to detect solid emboli could alert the patient to seek medical help sooner rather than later. A similar system could someday be used by astronauts during moon or Mars exploration in which an audio or a visual cue would alert the astronaut that bubbles were present in the midcerebral artery in time to take corrective actions.

Eliminating Decompression Sickness Through Engineering

An efficient exploration program needs an efficient EVA component. EVA preparation time should be minimized, and suit pressure should be low to accommodate EVA tasks without the wearer undergoing undue fatigue, physical discomfort, or even suit-related trauma. The atmosphere for Skylab achieved a working balance between risk and reward. The science and medical community accepted 70% O_2 at 5.0 psia, since the Earth-equivalent P_IO_2 would be 150 mmHg, and the risk of atelectasis was minimized, since the atmosphere was 30% N_2. Scientists on Earth did not have to provide a hypoxic or hyperoxic environment as part of their ground-based control studies, so μ*g* was the only experimental variable. No dedicated PB was needed before EVAs were undertaken from Skylab in spacesuits pressurized to 3.7 psia since the tissues would eventually equilibrate to a $P1N_2$ of no more than 1.2 psia, far below the suit pressure. Various restrictions, such as uncomfortable flame-retardant polybenzimidazole clothing, were imposed due to the serious risk of fire in a 70% O_2 atmosphere. Skylab was a success, and the need to confront several technical issues early in the mission showed that an effective EVA capability is critical to the success of long-duration missions.

Currently, a long PB time is needed before EVA from the shuttle or ISS. Denitrogenation may be effective to reduce the P(DCS), but even effective PB protocols are associated with a high incidence of VGE. Significant VGE insult of the lungs at 4.3 psia increases the chance of transporting VGE through the pulmonary vasculature or through a PFO.[153,219,220] A future habitat atmosphere should have a low ppN_2 to shorten or eliminate the PB time. One practical approach to reduce the ppN_2 is to increase the pO_2 while also reducing the ambient pressure.[29-31] A balance is achieved between the increased risk of fire at high O_2 concentration and the decreased risk of DCS as ppN_2 is reduced in the habitat. The concentration of O_2 and, therefore, the risk of fire for a given ambient pressure can be reduced further if P_IO_2 is less than 150 mmHg, but not so low as to cause significant hypoxia.[221] Not considered here are the many other factors involved in living in a low-pressure habitat with an exotic breathing mixture: a significant increase in electrical power for ventilation fans, increased insensible water loss (dehydration), valid issues about food preparation and steam sterilization,[222,223] problems with voice communication,[224] and reduced response time in the event of an atmosphere leak. The engineering, operational, scientific, and medical communities evaluate and "trade" various options until a safe system is devised. The program as a whole benefits from this trade process, but each stakeholder then mitigates what is lost in the trade process.

The Moon

A trade process was performed leading to the atmosphere recommendations[223] for the proposed NASA *Orion* crew exploration vehicle, *Altair* lunar surface access module (Figure 7), and lunar habitat. The atmospheric pressure and gas composition for these vehicles should minimize the in-suit PB time in preparation for EVA and reduce the risk of DCS. To accomplish this

objective and minimize the risk of fire, mildly hypoxic atmospheres were recommended.[221,223,225] The nominal atmosphere proposed for *Orion* is 10.2 psia with 26.5% O_2 (P_IO_2 of 127 mmHg), the atmosphere proposed for *Altair* is 8.0 psia with 32.0% O_2 (P_IO_2 of 117 mmHg), and the atmosphere proposed for the lunar habitat is 7.6 psia with 32.0% O_2 (P_IO_2 of 111 mmHg). The inclusion of a pressurized rover (Figure 8) as part of the integrated EVA system is a departure from the Apollo-era lunar exploration capability. Travel to distant places of geological interest is best performed in a pressurized vehicle that contains the *Altair* or a habitat atmosphere. This capability limits the time in the suit to just what is essential, which reduces the many hazards of being on the lunar surface. Validation of these atmospheres is a task for the future, and will be done with realistic EVA work tasks that include ambulation equivalent to walking in 0.17 Earth gravity (1*g*).[226]

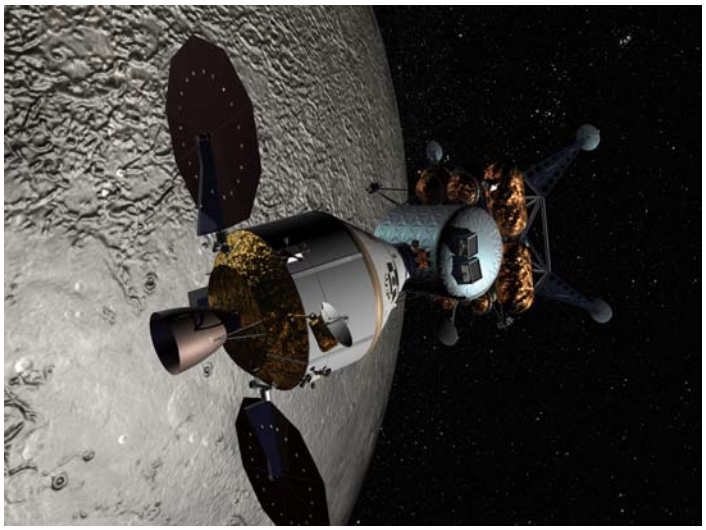

Figure 7. Artist's conception of *Orion* and *Altair* approaching the moon.

Figure 8. Prototype pressurized lunar rover with exterior-mounted spacesuits.

Mars and Beyond

Mars has something the moon lacks: a very thin atmosphere of 95.7% CO_2, 2.7% N_2, and 1.6% argon (Ar) exerting a pressure of about 5 mmHg. An automated vacuum pump that would be sent in advance of a crew would transfer a useful quantity of the thin atmosphere into a storage container. Carbon dioxide would be converted to O_2, leaving N_2 and Ar in a 1.68-to-1.0 ratio.[227,228] From an engineering standpoint, it is preferable to not separate inert gases into different containers, as this requires substantial energy and technology. Therefore, the atmosphere for the habitat would have N_2 and Ar in the same ratio as in the martian atmosphere, with the balance being O_2 to achieve an acceptable total pressure. Argon in the breathing mixture presents a special challenge to avoid DCS since it is twice as soluble as N_2, as clearly demonstrated by Pilmanis et al.[157] Using this atmosphere is a cost-effective alternative to transporting additional N_2 and O_2 from Earth. One example of an atmosphere for a Mars habitat is 8.0 psia total pressure with 32.0% O_2, 42.7% N_2, and 25.3% Ar. The operating pressure of the suit with 100% O_2 is set or even variable to complement the habitat atmosphere to maximize comfort, minimize final in-suit PB time, and reduce the P(DCS) to a level that can match the resources to treat DCS on Mars. The contribution of ambulation toward increased risk of DCS in martian gravity (0.37 Earth gravity) needs to be understood. Even if Ar is not selected for the habitat atmosphere, it would be available for the return trip to Earth since EVAs would not be a common occurrence during the transit to and from Mars.

Mining asteroids, permanent presence in low-Earth orbit, and even exploration of Titan[229] are all future possibilities. Flexibility in selecting both atmospheric gas composition and pressure plus advances in spacesuit design will enable humans to exploit space without interference from DCS.

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13. ABSTRACT *(Maximum 200 words)*

Among advances made during the 30-year operational life of the shuttle were those in our understanding of decompression sickness. New denitrogenation procedures were validated with research subjects in altitude chambers. Validation continued during hundreds of spacewalks that were safely performed from the shuttle and Russian Mir space station, and are performed from the International Space Station. Hypobaric exposure combined with microgravity achieved through space flight afforded a unique opportunity to understand more about decompression sickness. Lessons learned included: (1) greater understanding of limits to depressurization to minimize evolved gas and symptoms of decompression sickness, (2) methods to accelerate denitrogenation during oxygen prebreathing, (3) insights into tissue micronuclei formation and stability, (4) differences between research and operational settings, and (5) translation of research results into effective operational prebreathe protocols appropriate for a spacesuit operating at a pressure only 4.3 psia (222 mmHg) above the space vacuum. A spacewalk is the culmination of many hours of training under both hyperbaric and hypobaric conditions, training that must be managed to avoid decompression sickness. Flexibility in selecting atmospheric gas composition and pressure in future exploration vehicles and habitats plus advances in spacesuit design will enable humans to exploit space without interference from decompression sickness

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