

**Evidence Report:**

**Risk of Decompression Sickness (DCS)**

**Human Research Program  
Human Health Countermeasures Element**

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*Risk of Decompression Sickness (DCS)*

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## **1 PRD Risk Statement**

Given that tissue inert gas partial pressure is often greater than ambient pressure during phases of a mission, primarily during extravehicular activity (EVA), there is a possibility of decompression sickness (DCS).

## **2 Executive Summary**

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. Unlike other spaceflight related human risks, DCS is a known problem that has been mitigated since the first EVA. Various DCS mitigation strategies have effectively been used including a lower pressure high oxygen (O<sub>2</sub>) environment (Gemini, Apollo, Skylab) requiring a single 4-hr pre-launch O<sub>2</sub> prebreathe (PB); a resting 4-hr in-suit PB; an intermediate pressure, mildly hypoxic environment requiring a single 40- to 75-min in-suit PB; and several exercise-enhanced protocols combining both mask and in-suit PB. To date, DCS has been effectively mitigated through rigorous adherence to PB protocols validated specific to the EVA environment and primarily to the microgravity ( $\mu$ G) environment. While effective, these protocols can be complex and require significant pre-flight training, inflight crew time and consumables usage.

Historically, prebreathe protocols have been developed with the goal of preventing DCS and have been designed to meet operational needs. This operationally driven research has left gaps in knowledge about several DCS risk factors including bubble formation in space, nitrogen (N<sub>2</sub>) elimination in space, break in PB, micronuclei generation and tissue saturation across different pressure and gas environments.

The acceptable risk for DCS has been defined in the NASA Space flight Human-System Standard Volume 1, Revision A: CREW HEALTH.

### **Section 4.4.3.6.1 Decompression Sickness (DCS) Prevention.**

Nominal planned EVAs shall be performed using validated protocols that allow crewmembers to perform each EVA with a total risk of DCS  $\leq 15$  percent per person with 95% statistical confidence. Validated protocols shall meet the following historical criteria for acceptance based on ground studies:

- a. DCS  $\leq 15\%$  (includes Type I and cutis marmorata).
- b. Grade IV VGE  $\leq 20\%$ .
- c. No Type II DCS.

This DCS standard applies to the EVA section only and does not cover planned decompressions of a vehicle where the whole crew would be exposed to the hypobaric environment.

Therefore, the next step will be to develop and validate procedures, protocols, and countermeasures to meet this standard effectively and efficiently for the range of nominal and off-nominal atmospheres and decompression profiles that crewmembers may experience during future exploration missions. Utilization of the Exploration Atmosphere (8.2 psia / 34% O<sub>2</sub>), suit ports, variable pressure suits, and the inability to rapidly deorbit for medical treatment mean that existing DCS risk mitigation protocols and data sets are not applicable to future exploration missions. As of May 2016, a proposal has submitted to the Human Research Program (HRP) titled, “Validation of Exploration Atmosphere Prebreathe Protocol.” This HRP Directed Task proposal (HRP Master Task List ID# 1029) defined the need and methods for empirical validation of a new PB protocol that allows for safe and efficient exploration class EVAs and is currently awaiting completion of a directed task review.

To improve efficiency from a sea level atmosphere, data is needed on the potential differences in bubble formation and N<sub>2</sub> elimination while in  $\mu$ G. To improve safety and efficiency from any atmosphere, data is needed to describe the consequences of a break in PB. Finally, the opportunity exists to mitigate DCS primarily through engineering controls by the use of the 8.2 psia / 34% O<sub>2</sub> Exploration Atmosphere, suitport and variable pressure EVA suit. While promising, this strategy still requires validation to ensure it mitigates DCS risk to acceptable levels and to determine if there are any significant negative physiological effects associated with the Exploration Atmosphere’s mild hypoxia of approximately 4000-ft equivalent altitude.

### **3 Introduction**

*The overarching medical and operational philosophy is that it is better to prevent rather than to treat DCS.* The advent of technology that permitted a rapid change in ambient pressure ushered in the study of new medical conditions, such as DCS and hypoxia. Robert Hooke, an assistant researcher to Robert Boyle, created the first functional vacuum pump in 1671 (Harsch 2006). Much experimental work was done about exposure to a “rarified atmosphere.” Advances in the air compressor past the application of a bellows at the blacksmith’s hearth allowed for deeper diving beyond ones’ breath-holding ability and allowed for experiments under hyperbaric conditions. Paul Bert’s seminal treaties on barometric pressure codified in 1878 much of the empirical experience of the day (Bert 1878). Diving technology rapidly advanced that permitted deeper and longer exposures to hyperbaric air with the accompanying DCS on the return to 1 atmosphere absolute (ATA). Several textbooks about diving chronicle the history of diving and the methods to prevent DCS on return to 1 ATA and on treatment strategies to aid those afflicted with “the bends.” A compilation of experience with hypobaric, or altitude, DCS was published by Fulton in 1951, succinctly titled, *Decompression Sickness*. No other book has since been published to surpass the depth and breadth of information that lies between the covers of Fulton’s book. Much of what we know about hypobaric DCS and denitrogenation as a mitigation was learned during and shortly after World War II (WWII) and was summarized in Fulton’s book. Numerous chapters and reports have since been published that include new observations (evidence) for hypobaric DCS, summarized in the following pages.

Before the very first EVA, NASA understood that DCS was a risk to be mitigated. Given the highly constrained spaceflight environment, these mitigation strategies needed to be efficient

both in time and use of resources. A clear understanding of the mechanisms that cause DCS is needed to efficiently mitigate this potentially catastrophic risk to the mission and the astronaut. Should DCS occur in the spaceflight environment, it would occur during an EVA, when the crewmember is already isolated from the habitat in a physically constraining spacesuit. Historically, treatment for DCS can only begin once the EVA crewmember has terminated EVA activities and returned to the habitat to be repressurized.

### **3.1 DCS Signs and Symptoms**

DCS signs and symptoms are historically classified as Type I, Type II, and skin bends. At JSC, Type I symptoms are described as “pain only” DCS symptoms localized in muscle(s) or joint(s) and can include localized paresthesia and simple skin bends. Type I symptoms can result in an EVA termination/abort and jeopardize mission success. If not treated, Type I symptoms can eventually become incapacitating and jeopardize EVA crew member recovery. Type I incapacitating symptoms are generally preceded by less severe Type I symptoms.

Type II symptoms are systemic, generally neurological, involving the central nervous system; or cardiopulmonary, resulting in pulmonary “chokes”, circulatory collapse, shock, and even death; and may include multiple site paresthesias. Type II symptoms require immediate EVA abort and jeopardize both mission success and crew health. Type II symptoms may or may not be preceded by Type I symptoms and may be life threatening, especially in the EVA environment if not abated by an increase in pressure and adjunctive treatment.

Cutis Marmorata is a type of skin bends more serious than Type I skin bends where the skin has a marbled or mottled appearance. It likely indicates that significant bubble formation is occurring throughout the body. At JSC, this type of skin bends is categorized separately from Type I and Type II DCS.

DCS is also associated with gas embolism (the presence of gas bubbles in the vascular system), both venous gas emboli (VGE) and arterial gas emboli (AGE). Although VGE can typically be adequately filtered by the lung, circulating VGE is not a desired condition, especially with the presence of a patent foramen ovale (PFO), which is a hole in the wall separating the right and left atria of the heart. A PFO is a remnant of life in the womb where oxygenated blood from the placental circulation is shunted away from the pulmonary circulation of the fetus. This connection closes in most newborns, but about 25% of the adult population has some small patency (hole) that allows oxygenated and deoxygenated blood to mix. If denitrogenation is not effective, either due to inadequate vehicle design (either in gas constituency or atmospheric pressure, or a combination of both) or inadequate operational PB protocols, then the resulting presence of VGE during an EVA could cross through a PFO under particular conditions and become arterialized. Many factors in the aerospace environment compromise healthy lung function. These factors, when combined with a high number of VGE entering the pulmonary circulation, can put astronauts at high risk of arterializing VGE that are normally filtered by a healthy lung. AGE put the astronaut at risk of vascular blockages and resulting ischemic damage to brain or other organs.

Although the displacement of tissue by trapped gas spaces or the disruption of metabolic function due to embolic obstruction of blood flow can cause a wide range of signs and symptoms, the historical approach to DCS mitigation at NASA has been very conservative with the goal of preventing DCS. One consistent observation concerning test subjects at the Johnson Space Center (JSC) is that pain-only DCS after significant denitrogenation is predominately found in the lower body, particularly associated in or around the patella (Degner *et al.* 1965, Ryles & Pilmanis 1996).

## 3.2 Cause of DCS

There are two conditions necessary for the development of DCS. The first is inert gas supersaturation defined as a tissue inert gas partial pressure greater than ambient pressure. The second is the presence of a bubble nuclei (micronuclei) from which the supersaturated tissue inert gas can evolve into a gas bubble.

### 3.2.1 Supersaturation

A fundamental axiom about DCS is that a transient gas supersaturation, also called over-pressure or pressure difference ( $\Delta P$ ), 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  $\Delta P$  is positive:

$$\Delta P = \sum_{i=1}^n (P_i - P_2) \quad (\text{Eq. 1})$$

where  $P_i$  is the dissolved gas tension of the  $i^{\text{th}}$  gas of  $n$  species in the tissue and  $P_2$  is the ambient pressure after depressurization. The potential for bubble nucleation and rate of bubble growth are a function of the supersaturation.

Gas supersaturation in the tissue is not in itself harmful, but 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, whenever a gas space is formed due to partial or complete desaturation of a supersaturated tissue there is some probability of DCS [ $P(\text{DCS})$ ] (Weathersby *et al.* 1984). A necessary condition for DCS is the formation of a gas phase in the tissue. The assumption that pain results from the deformation of tissue past a critical point due to evolved gas 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, but the pressure difference between the gas space and the tissue. The pressure difference is termed “deformation pressure” by Nims (1951).



### 3.2.2 Bubble Nuclei (Micronuclei)

The previous discussion focused on reducing the amount of tissue N<sub>2</sub> to limit bubble growth, the classic Haldanean approach. But an emerging area of DCS prevention is to also hinder the transformation of tissue micronuclei into growing bubbles (Tikuisis & Gerth 2003, Blatteau *et al.* 2006). The presence of gaseous micronuclei in the tissues permits DCS under modest depressurizations (Weathersby *et al.* 1982). Information about and evidence for tissue micronuclei come mostly from indirect observations. The application of a high-pressure spike, either hydraulic or pneumatic, filtration, or ultracentrifugation of a sample are all accepted means to reduce the number and size of micronuclei (change the distribution), evident from fewer bubbles or cases of DCS after a subsequent depressurization (Evans & Walder 1969, Ikles 1970, Vann *et al.* 1980). One inference from these studies is that normal activity establishes a size distribution of micronuclei within tissues, which 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 (Hills 1977). A comprehensive review and discussion of micronuclei is not provided here, but information is available in Hills 1977, Hemmingsen 1989, Powell *et al.* 1993, 1995, Butler *et al.* 2006, Arieli *et al.* 2009, Hayward 1967, McDonough & Hemmingsen 1984, 1985, and Brubakk *et al.* 1989.

## 3.3 Situations of DCS

Humans are typically subjected to Earth-normal atmospheric pressure at sea level (1 ATA, 14.7 psia, 101.3 kPa, 760 mmHg) and Earth-normal gravity (1-G). This Earth-normal atmosphere is just one pressure in a range of higher and lower pressures where humans can comfortably exist. It is the rapid transition from higher to lower pressure that is the primary concern for DCS.

### 3.3.1 Diving (Ascent from Depth)

Long before humans could ascend to high altitude including space, they could dive to modest depths using compressed air or be exposed to modest depths through the application of caissons. Diving on compressed air or exposure to compressed air in a caisson allowed nitrogen (N<sub>2</sub>) to accumulate in tissues, based on the solubility of N<sub>2</sub> in the tissues and the delivery of N<sub>2</sub> by the circulatory system. Ascent limits for these “non-saturation” exposures were empirically derived based on avoiding supersaturation of mathematically derived tissue half-time compartments. The type (depth and duration) of the dive defined the controlling half-time compartments to limit the supersaturation specific to the compartment. Eventually divers would remain long enough at increased pressure to the point where no additional N<sub>2</sub> would be absorbed by the tissues at the new saturation depth; these are called saturation exposures. Ascent from saturation exposures are slower than for non-saturation exposures since the total dissolved N<sub>2</sub> is greater and the high N<sub>2</sub> partial pressure has come into equilibrium in tissues with long half-times, which require longer time to denitrogenate during ascent back to 1 ATA.

DCS is a known risk in the diving community and is mitigated through diver training and through the widespread use of decompression tables or dive computers, which determine dive time limits, ascent rates and decompression stops. Diving DCS is not the focus of this report. For

a more detailed discussion on diving DCS and dive physiology, the reader is referred to a text such as Bennett and Elliott's *Physiology and Medicine of Diving* (Brubakk and Neuman, 2003).

### **3.3.1.1 Diving Astronaut**

The focus of this evidence book is on preventing DCS during EVAs, but an EVA is just the culmination of many hours of training under both hyperbaric and hypobaric conditions. For ISS assembly EVAs, it was normal for a crewmember to train EVA procedures in the JSC Neutral Buoyancy Laboratory (NBL) at a ratio normally exceeding 10 NBL hours per 1 EVA hour (Williams and Johnson, 2003).

Policies and procedures are followed that minimize the P(DCS) after hyperbaric suited exposures in the 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. For example, the 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 hours. 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<sub>2</sub> and 54% N<sub>2</sub>. 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 the NBL's diving practices are available from Fitzpatrick & Conkin (2003).

Astronauts also train and maintain proficiency in operating the spacesuit under hypobaric conditions 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 (Horrigan *et al.* 1989, Vann *et al.* 1993, Pollock & Fitzpatrick 2004), 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 ([NASA JSC JPR 1800.3C](#)) returns astronauts to flight status after a successful treatment regime. Adherence to these policies and procedures, which undergo periodic review and update, minimize the chance that DCS will become a medical concern to the astronaut or will hinder the completion of training or safe execution of an EVA.

### **3.3.2 Ascent to Altitude / Depressurization to EVA Suit Pressure**

A diver experiencing DCS will do so upon return to the surface after completing their dive; treatment in such circumstances typically begins almost immediately and requires little action on the part of the patient. In contrast, an aviator that has lost cabin pressure or astronaut during an EVA in a spacesuit would be afflicted with DCS during the performance of their tasks. These tasks are left unfinished and the aviator/astronaut must typically return themselves or be returned to a safe environment and configuration by a co-pilot or EVA buddy before treatment for evolved gas can be initiated. Thus, in addition to the health risk associated with any occurrence of DCS, an occurrence of DCS during spaceflight carries the additional risk associated with delayed initiation of treatment as well as the secondary concern of the potential for loss of productivity.

The most effective way to reduce P(DCS) is to reduce the  $\Delta P$  between environments (described in Eq. 1), by reducing  $P_i$  (cabin inert gas [primarily  $N_2$ ] partial pressure) or increasing  $P_2$  (suit pressure), or some combination of both to achieve acceptable risk and operational efficiency. A spacesuit is a flexible spacecraft, and details about U.S. spacesuits are available from Thomas and McMann (2011). The current NASA spacesuit, called the Extravehicular Mobility Unit (EMU), operates at 4.3 psia, or 222 mmHg, above the vacuum of space (Powell *et al.* 1994a, Locke 2008). Current EMU suit technology, especially in the design of gloves, does not permit a high pressure suit without increased fatigue, reduced mobility and decreased manual dexterity, whereas the Russian Space Program accepts some of these human performance decrements and operates the Orlan suit at 5.8 psia. Historically, reducing the risk of DCS by increasing suit pressure has implied significant operational limitations, but developments are underway to develop a flight-ready variable pressure suit capable of operating effectively between 3.7 and 8.2 psia.

### **3.4 Definition of Acceptable Risk for DCS**

: DCS is a known risk during EVA that requires mitigation. Elimination of all risk through a lengthy PB prior to EVA is both impractical and virtually impossible to demonstrate due to the probabilistic nature of DCS. An alternative approach to engineering out DCS as a risk is to define acceptable risk. This approach necessitates the development of a standard of acceptable DCS risk for which countermeasures can then be evaluated against. This critical step of defining the acceptable level of DCS risk began as the initial step of the Prebreathe Reduction Program in 1997 with participation from the NASA EVA community, United States Navy, United States Air Force and academic research community.

Some of the major factors considered in this process included:

- DCS risk per EVA based on flight, ground and modeled data
- On orbit DCS treatment capability
- Disposition of an astronaut that reports DCS
- NASA EVA community awareness of DCS
- Availability of EVA crewmembers to successfully complete the assembly of the ISS\

The final product of this effort was the NASA DCS Risk Definition and Contingency Plan, which led to the development of the following:

- Acceptable DCS Risk for the development of ISS PB Protocols – All protocols had to demonstrate total DCS < 15 percent at 95% Confidence Limit (CL), < 20 percent Grade IV VGE at 95% CL, No Type II (Serious) DCS).
- EVA Cuff Checklist that attaches to the cuff of the arm during EVA, which specifies a sequence of actions in the event of symptoms. This Cuff Checklist was not DCS specific, but rather provided instructions in the case of symptoms such as pain or paresthesia irrespective of whether the symptoms were caused by DCS or suit related trauma.
- DCS Disposition Policy that mandated the reporting of DCS symptoms both on the ground (chamber or NBL operations) and described the process by which an astronaut or would be evaluated and returned to flight status.

## *Risk of Decompression Sickness (DCS)*

This level of acceptable DCS risk used for the PB reduction program was used in the validation of 3 additional PB protocols, which were used to successfully assemble the ISS and are still used to perform ISS maintenance EVAs. By validating operational PB protocols against this acceptable risk level, NASA has successfully prevented both serious Type II DCS and Type I pain only DCS. This acceptable risk level was reviewed by several JSC Human Health and Performance Directorate Boards and the NASA Headquarters Chief Health and Medical Office and subsequently included as a new human spaceflight standard in the EVA section of NASA-STD-3001 Volume 1. This standard dictates the minimum standard for which all future PB protocols will need to test against. The focus of this standard was to protect against long and short term human health consequences, but it does not define any guidelines for expected EVA efficiency, crew time or consumables.

The acceptable risk for DCS is defined in the NASA Space flight Human-System Standard Volume 1, Revision A: CREW HEALTH.

### Section 4.4.3.6.1 Decompression Sickness (DCS) Prevention.

Nominal planned EVAs shall be performed using validated protocols that allow crewmembers to perform each EVA with a total risk of DCS  $\leq 15\%$  per person with 95% statistical confidence. Validated protocols shall meet the following historical criteria for acceptance based on ground studies:

- a. DCS  $\leq 15\%$  (includes Type I and cutis marmorata).
- b. Grade IV VGE  $\leq 20\%$ .
- c. No Type II DCS.

This DCS standard applies to the EVA section only and does not cover planned decompressions of a vehicle where the whole crew would be exposed to the hypobaric environment.

While this DCS standard established a minimum threshold for protecting crew from DCS during EVA, it does not describe acceptable risk for vehicle decompressions such as when the crew would transition from a normobaric atmosphere to the Exploration Atmosphere (8.2 psia, 34% O<sub>2</sub>, balance N<sub>2</sub>). The primary difference in this case is that the whole crew is exposed to DCS risk at the same time. An additional metric to consider would be the acceptable risk for contingency EVA scenarios. Currently, all contingency scenarios are handled as isolated events, but a pre-determined level of acceptable risk for contingency EVA and a supporting higher risk, but lower overhead PB protocol should be considered.

## **4 Spaceflight Evidence of DCS**

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 (Conkin *et al.* 2003). How are these disparate observations reconciled? Technicians have reported pain-only DCS at JSC during suit development (two cases are documented in an internal NASA Investigation Report from 1988), and at least 1 astronaut recollected pain (considerably after the spaceflight) in a knee on 2 occasions after depressurization to 5.0 psia in the spacecraft (Hawkins & Zieglschmid 1975). Foster & Butler (2009) discussed several factors related to working in a hypobaric and

$\mu$ G environment that may reduce the P(DCS) in EVA astronauts, which are summarized in this section.

## **4.1 Potential Bias to Not Report DCS Symptoms**

A research setting designed specifically to monitor for DCS is different from an operational setting where a highly trained and motivated crewmember is performing an EVA, which is considered one of the pinnacles of an astronaut's career. Even if DCS symptoms have occurred, there may be a bias to not report mild discomfort in this type of an operational setting, especially if symptoms are not limiting. NASA's current policy is that every test subject and every crewmember who participate in hyperbaric or hypobaric operations are required to immediately report the onset of any DCS symptoms ([NASA JSC JPR 1800.3C](#)).

Under-reporting of DCS symptoms is routinely observed in pilot training where qualification to fly is compromised if DCS is reported during hypobaric training activities. This is discussed relative to the high-altitude U-2 pilot community (Bendrick *et al.* 1996 and Hundemer *et al.* 2012), which highlight differences between operational and research reports of DCS. In Bendrick *et al.* (1996), 75% of 273 active duty and retired U-2 pilots responding to an anonymous questionnaire said that they had DCS symptoms at least once during their careers flying U-2 aircraft, but rarely reported their symptoms to the Flight Surgeon (Meader 1967). Webb *et al.* 1996 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 (Hankins *et al.* 2000).

The only anecdotal report of a DCS symptom in an astronaut during spaceflight was reported several years after the flight in a personal autobiography rather than real-time to the flight surgeon (Hawkins & Zieglschmid 1975). For various reasons, astronauts and pilots are not motivated to report every small discomfort (Jersey *et al.* 2010). As a result, it is possible that the first report of DCS during an EVA will be a serious case of DCS (Conkin 2001).

## **4.2 Masked DCS Symptoms**

There are valid reasons why mild symptoms of DCS might be masked during an EVA. 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. As such, many mild cases of DCS that are not reported during EVA could be attributed to pain caused by working in the EMU. Since mild symptoms quickly clear during repressurization, 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 (Waligora *et al.* 1984, Conkin *et al.* 1990). About 85% of those with 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. Because 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.

### **4.3 Operational and Gravitational Benefits of the Spaceflight Environment**

It is also possible that DCS has not actually occurred during EVA (Powell *et al.* 1995, Gernhardt *et al.* 2004). Subjects wearing an O<sub>2</sub> mask and otherwise comfortable in a shirtsleeve environment at 1-G are not the same as astronauts surrounded by 100% O<sub>2</sub> and maneuvering in  $\mu$ G with limited mobility and uncomfortable spacesuits. Limited motion in the *Orlan*, and by extrapolation the EMU, is hypothesized to be a significant factor to reduce the likelihood of DCS during an EVA.

Astronauts perform more conservative prebreathing in space 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. Based on detailed analysis of actual prebreathe performed on-orbit, Tissue Ratio (TR), or R-value computed for the first 142 staged PB protocols from the Shuttle was  $1.51 \pm 0.07$  SD compared to  $1.52 \pm 0.26$  for 245 research subjects at JSC with 18% DCS, who were ambulatory during testing (Conkin *et al.* 2006). Ambulation encourages DCS and VGE from the lower body, so the absence of ambulation in  $\mu$ G likely reduces the incidence of DCS below 18% during EVA (Conkin *et al.* 2006). During the Shuttle staged protocol, TR also decreases during subsequent EVAs, from 1.51 to 1.48 for the second EVA. This is because breathing 100% O<sub>2</sub> during a 6 hr EVA continues the denitrogenation over multiple EVAs during a Shuttle mission, and because the crew lives at 10.2 psia / 26.5% O<sub>2</sub>, where tissues eventually equilibrate to a pN<sub>2</sub> of about 7.5 psia. Waligora & Pepper 1995 and Waligora & Kumar 1995 summarized physiological aspects of working in space during the first 59 Shuttle person-EVAs.

In addition to added PB duration, we also need to understand if the primary risk mitigation strategy of prebreathing is more or less affected by adaptations to  $\mu$ G. All astronauts undergo adaptation in  $\mu$ G (Nicogossian & Parker 1982). About 2 liters of fluid from the lower extremities is redistributed into the chest and head, with a resulting decrease in total body water. The 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 of this fluid shift, denitrogenation in  $\mu$ G may be more efficient than on Earth if a supine body position is a reasonable analog for  $\mu$ G (Balldin 1973).

Lesser interventions than adaptation to  $\mu$ G are known to modify N<sub>2</sub> washout (Pendergast & Olszowska 1989, Margaria & Sendroy 1950). Jones *et al.* (1945) did the early work to understand the effects of blood perfusion on N<sub>2</sub> uptake and elimination in tissues. Behnke *et al.* (1935, 1937, 1941) showed how body composition and exercise during PB influenced N<sub>2</sub> removal. Studies by Balldin *et al.* (1971, 1972, 1973, 1978) showed how increased ambient temperature, supine body position, and immersion in water increased N<sub>2</sub> removal from adipose and muscle tissue, and from the entire body. Theis *et al.* 1979 confirmed and supplemented these data by examining whole-body N<sub>2</sub> washout during supine body position. Balldin & Borgstrom 1977 and Curry & Lundgren 2003 reported that even negative-pressure breathing accelerates N<sub>2</sub> washout. The most recent efforts to understand N<sub>2</sub> removal under various experimental conditions, including  $\mu$ G simulation, were by Vann & Gerth 1995 and Gerth *et al.* 1987, 1989. Various experimental interventions resulted in a wide range of tissue N<sub>2</sub> washout

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from about 8 ml/kg for seated subjects to about 24 ml/kg for subjects who performed 50 watts of continuous arm and leg exercise for 2 hr while in a 6-degree head-down tilt during a 3 hr PB. So it is reasonable to hypothesize that the altered physiology and anatomy in response to  $\mu\text{G}$  adaptation modifies in an unknown way the amount of  $\text{N}_2$  removed from the body during PB (Conkin *et al.* 1983, Powell *et al.* 1992, Conkin & Powell 2001).

For some of any operational PB, and all of the EVA the astronaut is surrounded by 100%  $\text{O}_2$ . It is unclear how much  $\text{N}_2$  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 (Groom & Farhi 1967). Warm ambient temperature enhances denitrogenation (Ballardin 1973). Astronauts in the Shuttle and during 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 astronauts. It is unclear how skin temperature that is cool due to the Liquid Cooling and Ventilation Garment affects the transport of  $\text{N}_2$  across the skin during the in-suit portion of the PB and during the EVA. Knowing anything conclusive about  $\text{N}_2$  washout in space or the unbiased information from an in-suit Doppler bubble detector would greatly help to understand the true risk of DCS in EVA astronauts (Barer *et al.* 1995a, Conkin *et al.* 1996a, Conkin *et al.* 1998, Thompson *et al.* 2002).

Astronauts are physically active during PB, and exercise during PB accelerates  $\text{N}_2$  washout (Loftin *et al.* 1997, Webb *et al.* 1996, Pendergast *et al.* 2012). Subjects in early trials at JSC were inactive during their PB. Aerobic fitness, as measured by  $\text{VO}_2$  peak, is not *per se* associated with resistance to pain-only DCS. An analysis of  $\text{VO}_2$  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 (Conkin *et al.* 2007, Pollock *et al.* 2004a). The benefit of exceptional aerobic fitness toward reducing the P(DCS) is only realized when exercise is exploited as part of the PB. A person with low  $\text{VO}_2$  peak can reduce their P(DCS) to match a fit person by increasing the intensity of exercise in the same PB time, by increasing the length of the PB, or some combination of both (Conkin *et al.* 2007, Conkin *et al.* 2004).

Cumulative  $\text{O}_2$  consumption during PB is not the only consideration to reduce the P(DCS). Effective  $\text{N}_2$  elimination seems to depend on how the exercise is performed more so than just total  $\text{O}_2$  consumption per unit time normalized to body mass. And there are constraints as to the type and duration of exercise 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 when exercise during PB was prescribed as % $\text{VO}_2$  peak (Conkin 2010). 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  $\text{VO}_2$  peak. Therefore, subjects who would be aged matched to the astronaut population would be less fit. If fitness is linked to DCS susceptibility (Webb *et al.* 2005, Carturan *et al.* 1999, 2002), then astronauts as a group under any PB condition may be less susceptible to DCS than subjects of comparable age (Conkin *et al.* 2003). Finally, the “effective” exercise in the EMU might be less than or different from exercise on Earth used to simulate EVA activity, and exercise is certainly an important consideration for DCS risk at altitude.

## **4.4 Current ISS DCS Mitigations**

Different missions require different strategies to avoid DCS. In every case, a detailed analysis (trade process) eventually defines the appropriate PB. We provide a summary of PB protocols that are currently in successful use, along with any lessons learned along the way. ISS astronauts currently have available three denitrogenation *strategies* to reduce the P(DCS): resting PB, staged denitrogenation, and exercise PB.

Desire to perform science with  $\mu\text{G}$  as the primary variable led 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 (brief exposure to high partial pressure of  $\text{N}_2$  ( $\text{pN}_2$ )) during a 100%  $\text{O}_2$  PB is unavoidable if transitioning  $\text{O}_2$  delivery from a shirt-sleeve mask to the EVA suit. This requires research to understand and procedures to compensate for air breaks in PB.

### **4.4.1 In-suit 4 hour Prebreathe**

In the simplest resting PB protocol, the astronaut breathes 100%  $\text{O}_2$  in the spacesuit for 4-hrs. The 4-hour duration was determined as being necessary to achieve an acceptable P(DCS) based on the type and amount of work to be done in the suit and the duration of the hypobaric exposure (Conkin *et al.* 1987). The operational challenge is to match the length of PB with an acceptable low incidence of DCS (Waligora *et al.* 1987) to produce an efficient EVA system. Waligora *et al.* 1984 describes tests of 3.5 and 4 hr PBs at JSC, which evolved into the current operational 4-hr in-suit PB. The 4-hr in-suit PB has been used 6 times during spaceflight with no reported DCS. A 4-hr prebreathe immediately prior to performing an EVA that could last up to 8 hours represents an inefficient use of crew time, makes the crew duty day over 14 hours on EVA days, and inefficiently uses up suit consumables.

### **4.4.2 Campout Protocol**

A modification of the Shuttle staged protocol, called the campout protocol, significantly reduces the required in-suit PB duration by having the two EVA crewmembers “camp out” in the ISS airlock at 10.2 psia, 26.5%  $\text{O}_2$  during the night prior to their EVA. 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 personal hygiene facilities in the airlock means that a post-sleep repressurization to 14.7 psia is required prior to suit donning. During this break, the 2 astronauts breathe 100%  $\text{O}_2$  by mask for 70 min while gathering food and using the restroom. Upon return to 10.2 psia, 26.5%  $\text{O}_2$  the masks are removed, and the suit-donning process is completed. The airlock is repressurized 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 the final depressurization of the airlock to the vacuum of space with the suits remaining at 4.3 psia.



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After extensive review, the similarity of the campout PB to the Shuttle staged PB (described in Section 4.5.1) along with good operational experience with the Shuttle staged protocol negated an empirical validation of the campout PB. The first EVAs from the ISS using the campout protocol took place in September 2006 with 146 person-EVAs completed since that point with no reports of DCS. The last use of Campout was 05/06/11 although it is still currently available for ISS crewmembers.

This more complicated staged PB protocol was 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 unproductive during a 4 hour in-suit 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 the majority 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<sub>2</sub> purge and leak check, the transition from a mask, or even a mouth piece and nose clip, to the suit with 100% O<sub>2</sub> without an air break has proven unavoidable.

### 4.4.3 Exercise Prebreathe: CEVIS and ISLE Protocols

After the ISS *Quest* 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. An accelerated denitrogenation protocol was needed to avoid scheduling constraints on EVAs performed from the ISS and since N<sub>2</sub> elimination and uptake is a perfusion-limited process, the use of exercise during the PB is an effective method of accelerating denitrogenation. 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 done with hatches closed between the 2 vehicles so that the 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 WW II (Behnke & Willmon 1941, Webb *et al.* 1943, Boothby *et al.* 1952), and reevaluated at Brooks Air Force Base (AFB) for the special operations community (Webb *et al.* 1989, 1996, 1998, 2002, 2004, Hankins *et al.* 2000) and most recently by NASA. Details are available for 9 exercise PB options evaluated by NASA from 1997 to 2009 in Gernhardt *et al.* 2000, 2003, Conkin *et al.* 2004, and Loftin *et al.* 1997 (also see Table 3).

Two exercise PB protocols acceptable for operations on the ISS are briefly described: the Exercise PB protocol using the cycle ergometer with vibration isolation and stabilization (CEVIS) device and the In-suit Light Exercise (ISLE) PB protocol using the EMU as a resistive exercise device.

#### **4.4.3.1 Cycle Ergometer with Vibration Isolation and Stabilization (CEVIS) Protocol**

For the CEVIS Exercise PB protocol, prior to launch the astronaut performs a peak O<sub>2</sub> consumption (VO<sub>2</sub>) test using leg ergometry, and a linear regression of VO<sub>2</sub> versus watts (work-load) is created for that individual. An exercise prescription is produced that distributes the appropriate work-load between the upper body (12%) and lower body (88%).

During on-orbit EVA preparations, the astronaut breathes O<sub>2</sub> from a mask and performs 3 min of incremental exercise on the CEVIS at about 75 revolutions per min using a prescription that increases work from 37.5%, to 50.0% and then to 62.5% of their VO<sub>2</sub> peak while also rhythmically pulling against elastic surgical tubing to include upper body activity. The ergometry is complete after an additional 7 min at 75% of VO<sub>2</sub> peak.

After waiting an elapsed time of 50 min while still breathing 100% O<sub>2</sub> from the mask, the EVA astronauts and the IVA crewmember depressurize in the ISS airlock to 10.2 psia in 30 min. During the depressurization, the liquid cooling garment and the lower portion of the spacesuit are donned. Once the airlock O<sub>2</sub> concentration stabilizes at 26.5%, the astronauts and IVA crew attendant remove the masks and complete the donning of the upper torso of the spacesuit. Thus, for a significant portion of the PB duration the astronaut is physically active in the suit-donning process. A leak check and then a purge with 100% O<sub>2</sub> to remove N<sub>2</sub> from the suit completes the suit-donning procedure.

The in-suit PB starts in conjunction with a 5-min repressurization back to 14.7 psia where the remaining 55 min of in-suit PB is performed and the IVA crewmember exits the airlock. The final depressurization of the airlock to the vacuum of space and to 4.3 psia in the suit takes 30 min. The CEVIS Exercise PB has been used 52 times as of 05/06/16 with no reported DCS and was last used 11/21/09 after a false alarm interrupted the Campout protocol causing the crew to alter plans and change PB protocols to preserve the EVA.

#### **4.4.3.2 In-Suit Light Exercise (ISLE) Protocol**

For the ISLE PB protocol, the astronaut does not perform a short bout of intense PB exercise on the CEVIS prior to suit donning at 10.2 psia but instead performs a longer period of mild exercise in the EMU. The ISLE protocol shares many steps with the Exercise PB protocol but differs in that 40 min are spent breathing 100% O<sub>2</sub> by mask followed by a 20 min depressurization to 10.2 psia. Once suit donning is complete, arm and leg motions are performed for 4 min followed by 1 min of rest in conjunction with a 5-min repressurization back to 14.7 psia. The mild exercise pattern continues for 50 min and achieves a minimum VO<sub>2</sub> of 6.8 ml·Kg<sup>-1</sup>·min<sup>-1</sup>. An additional 50 min of resting PB completes the protocol followed by a 30 min depressurization of the airlock to vacuum. The ISLE PB is currently the prime protocol used by the ISS and has been used 40 times as of 05/06/16 with no reported DCS.

#### **4.4.3.3 Combining Exercise with Intermittent Recompression**

The return to 14.7 psia after a short suit donning period at 10.2 psia in both the Exercise and ISLE PB protocols, and 2 returns to 14.7 psia over the course of the longer campout PB likely reduced the subsequent P(DCS) through removal of silent bubbles. These bubbles had the

potential to form from a limited number of large-radius micronuclei during the initial depressurization to 10.2 psia. Once formed and then reabsorbed during the repressurization to 14.7 psia while breathing 100% O<sub>2</sub>, the tissues are temporarily left with a smaller range of micronuclei radii from which to grow bubbles during the final depressurization to 4.3 psia. This did not occur during the Shuttle 10.2 psia staged depressurization protocol. The entire habitable volume of the Shuttle was depressurized, so the astronauts simply continued the depressurization from 10.2 psia to 4.3 psia after suit donning in the airlock.

## **4.5 Retired Prebreathe Protocols**

The remainder is a brief historical summary of PB protocols that were successful, with lessons learned along the way.

### **4.5.1 Shuttle Staged Protocol**

In the Shuttle staged denitrogenation strategy, the ambient pressure was decreased to an intermediate pressure so that the inspired partial pressure of N<sub>2</sub> (P<sub>I</sub>N<sub>2</sub>) was lower than the initial P<sub>I</sub>N<sub>2</sub> (Allen *et al.* 1969, Maio *et al.* 1970, Cooke & Robertson 1974, Horrigan & Waligora 1980, Waligora *et al.* 1983). The staged depressurization approach is enhanced when O<sub>2</sub> concentration is also increased to lessen the impact of hypoxia and to further reduce P<sub>I</sub>N<sub>2</sub>. However, the initial pressure reduction could transform a subpopulation of tissue micronuclei into “silent” bubbles, so a 60 min PB with a mask was performed before the initial modest reduction in ambient pressure to 10.2 psia (Damato *et al.* 1963, Degner *et al.* 1965, Vann & Torre-Bueno 1984, Waligora *et al.* 1984, Hills 1985).

This protocol that ultimately became the preferred PB for the Shuttle was achieved in 3 steps:

1. Initial 60 min PB by mask, of which 45 min was completed before the Shuttle atmosphere was depressurized from 14.7 psia to 10.2 psia and the air was enriched to 26.5% O<sub>2</sub> to provide an inspired partial pressure of O<sub>2</sub> (P<sub>I</sub>O<sub>2</sub>) of 127 mmHg.
2. Minimum stay of 12 hr at this intermediate pressure.
3. 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.

Figure 1 shows the cumulative fraction of VGE first detected in subjects exposed to 4.3 psia for 4 hr after 3 different PBs. A related figure appears in Waligora *et al.* 1984 (their Figure 12). All subjects performed EVA-simulation work activities and were ambulatory at 4.3 psia. The solid line that increases (steps) and plateaus quickly to about 45% is from 10 of 22 subjects that had VGE with a mean onset time of  $43 \pm 43$  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<sub>2</sub>. 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  $105 \pm 48$  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  $115 \pm 55$  min. The mean VGE onset times were statistically longer ( $p < 0.002$ ) when compared to the trial without the 1 hr PB before ascent to 10.2 psia for 12 hr.

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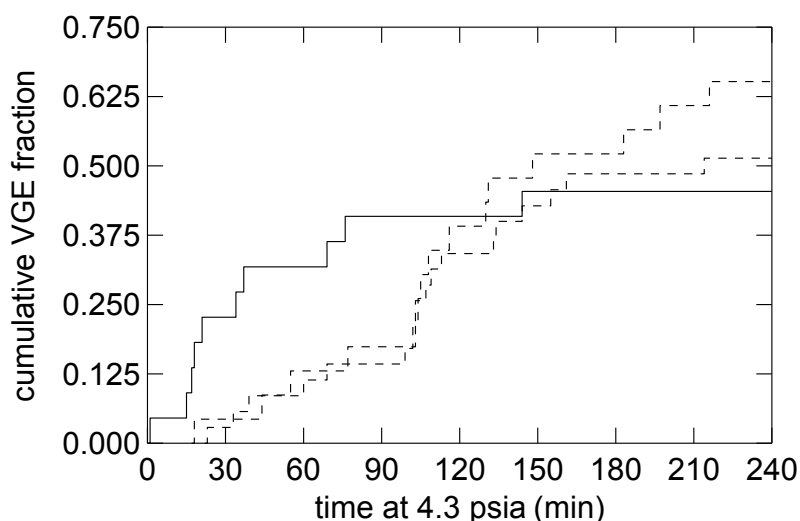


Figure 1. The onset time for the first detection of VGE was earlier in a trial (Test 2b) where no PB was performed before the first ascent and subsequent 12 hr exposure to 10.2 psia (solid line) compared to when a 1 hr PB was performed (50% peak, Test 3b) or when there was a direct ascent to 4.3 psia 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 ready to grow and enter the venous circulation after the final depressurization to 4.3 psia. An ascent to only 10.2 psia (3,000 m, 9,750 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 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 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<sub>2</sub> atmosphere, since the vehicle was not planned to operate under these conditions. Several interacting variables were evaluated in isolation or in combination: rate of ascent to intermediate pressure, the intermediate pressure itself (equipment cooling issues, Horrigan *et al.* 1985), the pO<sub>2</sub> and pN<sub>2</sub> at the intermediate pressure (hypoxia and flammability issues, Waligora *et al.* 1982), length of stay (Damato *et al.* 1963, Waligora *et al.* 1983), likelihood of silent bubbles, final suit pressure, duration of EVA, work performed in the suit, the final in-suit PB time before final ascent, and balancing the acceptable risk of DCS during EVA with limited treatment options (Adams *et al.* 1981, Waligora *et al.* 1984).

The time at 10.2 psia and 26.5% O<sub>2</sub>, was not a break in PB since the lengthy exposure to a reduced pN<sub>2</sub> 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 repressurize to 14.7 psia. If the time spent at 10.2 psia was expected to be greater than 36 hr, then 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. Although this procedure was complicated and had several operational and physiological impacts, it was preferred over the simpler but less efficient 4-hr in-suit PB. The first EVAs that used the Shuttle staged protocol were on STS-41B in February 1984, and the last of 153 person-EVAs was in 2011 with the retirement of the Shuttle.

#### 4.5.2 Skylab

Skylab provided a unique environment from which to conduct studies on adaptation to  $\mu$ G. The atmosphere for Skylab achieved a working balance between risk and reward. The science and medical community accepted 70% O<sub>2</sub> at 5.0 psia since the Earth-equivalent P<sub>i</sub>O<sub>2</sub> would be 150 mmHg, and the risk of atelectasis was minimized since the atmosphere was 30% N<sub>2</sub>. Scientists on Earth did not have to provide a hypoxic or hyperoxic environment as part of their ground-based control studies, so  $\mu$ G was the primary experimental variable. No dedicated PB was needed before EVAs from Skylab in spacesuits pressurized to 3.7 psia since the tissues would eventually equilibrate to a computed tissue N<sub>2</sub> partial pressure (P<sub>1</sub>N<sub>2</sub>) 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<sub>2</sub> atmosphere. But Skylab was a success, and the need to confront several technical issues early in the mission showed that an effective EVA capability was critical to the success of long-duration missions.

#### 4.5.3 Apollo and Gemini

A minimum 3-hr in-suit PB was performed before launch in all NASA programs prior to the Shuttle (Maio *et al.* 1970). This protected inactive astronauts from DCS after reaching orbit; during ascent cabin pressure was reduced from 14.7 psia to 5.0 psia and the atmosphere was simultaneously enriched to 100% O<sub>2</sub> (Powell *et al.* 1994a). 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<sub>2</sub> atmosphere as the missions proceeded (Hawkins & Zieglschmid 1975). This was not an unexpected outcome based on prior PB validation trials reported by Maio *et al.* 1969, 1970. Astronauts on subsequent EVAs from the Apollo spacecraft, Skylab, and on Moon walks from the Lunar Module in suits pressurized to 3.7 psia were not at risk for DCS due to denitrogenation achieved during their extended time in the hypobaric and hyperoxic breathing environment.

### 4.6 DCS Modeling Evidence

Probability models are critical to the understanding and mitigating DCS risk. These models are first developed as statistical descriptions of DCS incidence from a given data set and eventually

predict DCS incidence effectively over a given boundary of input parameters. Certain DCS models will be described in the section and Appendix A is provided for a comprehensive summary of DCS model details. Models are typically used to develop potential PB protocols, which are then tested on the ground in hypobaric EVA simulations to ensure that the protocol achieves acceptable DCS risk level. DCS models assess impacts to ground validated protocols which are often modified during the transition from research to operations. In these cases, the models are used to ensure that changes to the validate protocol are neutral or in favor of enhanced crew safety. In some cases, DCS probability models, in conjunction with expert opinion, have been used in place of ground testing to accept a PB protocol; which was the case with the Campout PB.

In addition to statistically driven probability model, a decompression dose can also be computed from a biophysical model about bubble growth, such as the maximum size a theoretical bubble achieves, the rate of growth of the bubble, or the summed volume from a collection of bubbles competing for inert gas (Tikuisis & Gerth 2003, Srinivasan *et al.* 2003).

#### 4.6.1 Tissue Ratio

Fundamental to understanding 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 by Haldane to define the limit to direct ascent for divers at the end of the 19<sup>th</sup> century. The reader is referred to Stepanek & Webb (2008) for the historical background on TR.

TR is the ratio of computed  $P_{1N_2}$  in a theoretical tissue to ambient pressure. Equation 2 defines  $P_{1N_2}$  and  $P_2$  is the ambient pressure after depressurization. Prebreathing 100%  $O_2$  or  $O_2$ -enriched mixtures before a hypobaric exposure reduces P(DCS), so it is necessary to account for the use of  $O_2$ -enriched mixtures as part of the expression for decompression dose. After  $pN_2$  in the breathing mixture changes, such as during a switch from ambient air to a mask supplied with 100%  $O_2$ , the  $pN_2$  that is reached in a designated tissue compartment after a specific time is  $P_{1N_2}$ :

$$P_{1N_2} = P_0 + (P_a - P_0) (1 - e^{-k t}), \quad (2)$$

where  $P_{1N_2}$  is calculated for the tissue after  $t$  min,  $P_0$  is the initial  $pN_2$  in the compartment,  $P_a$  is the ambient  $pN_2$  in the breathing mixture, and  $t$  is the time at the new  $P_a$  in min. The tissue rate constant  $k$  is equal to  $\ln(2) / t_{1/2}$ , where  $t_{1/2}$  is the half-time for  $pN_2$  in the 360 min compartment. The particular half-time compartment is a statistical construct that optimizes TR as decompression dose to the observed dichotomous DCS or VGE outcomes from a collection of trials (Vann *et al.* 1987). Different half-time compartments reflect the varying rates at which different body tissues take up and eliminate inert gases. For example fast 5- and 10-minute half-time compartments are used to represent the brain and spinal cord, which are highly perfused and rapidly take-up and eliminate inert gases. A long 360 min half-time is associated with long PB times tested by NASA (Conkin *et al.* 1996). A shorter half-time combined with long PBs produce 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 3 describes the simple case where  $P_a$  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. 3 covers these cases. One novel application is to reduce  $N_2$  content through time as dictated by the operational time-line 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  $O_2$ . The cost likely exceeds the rewards with this approach, so 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 (Conkin *et al.* 2004).

Equation 3 is one form of TR as decompression dose, which approximates the potential volume at ambient pressure of  $N_2$  evolved in a unit volume of tissue given that all the available  $N_2$  at  $P_2$  has transformed from the dissolved state to the evolved state (Conkin 1994, Conkin *et al.* 1998):

$$\text{decompression dose} = [(P1N_2 / P_2) - 0.79], \quad (3)$$

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

TR is an index of the true decompression dose, and 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 versus TR dose-response curve would be nearly flat over a range of TR to, say, 1.1. The flat region is an indication that decompression dose must exceed some critical value. TR is utilitarian, 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, but this R-value of 1.65 in an EMU does not mean the  $P(\text{DCS})$  is zero (Conkin *et al.* 1990, Kumar & Powell 1994).

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  $P(\text{DCS})$  that is the equivalent of the  $P(\text{DCS})$  in the EMU, so the acceptable R-value (TR) is not an absolute, but in this case is a function of the suit pressure (Conkin *et al.* 1996, Chadov *et al.* 1996). The DCS research and operational EVA experience in the Russian space program is too extensive to summarize here (Barer 1995a) and parallels the efforts in the U.S. space program.

#### 4.6.2 Statistical and Biophysical Models

The integration of biophysical models of tissue bubble dynamics with statistical models of DCS and VGE outcomes from hypobaric exposures using logistic regression or survival analysis has led to significant advances in the development of probabilistic risk models in the last 20 years. For example, estimating a DCS risk model requires data that contains (1) the dichotomous

DCS outcome (presence or absence) for multiple test results obtained over various experimental conditions, (2) explanatory variables such as decompression dose, which categorize or describe the experimental conditions and (3) demographic information pertaining to the test subjects. With this data, one can then estimate a risk model with logistic regression where the probability of DCS is expressed as logistic function or Hill equation with dose as input.

Simple descriptions of decompression dose such as TR or  $\Delta P$  approximate the true dose (Weathersby & Homer 1984, Conkin 1994) whereas models about tissue bubble dynamics strive to define the true dose through diffusion-based physics and consideration of mass-balance (Epstein & Plesset 1950, Van Liew & Hlastala 1969, Gernhardt 1991, and more recently Gerth & Vann 1997, Thalmann *et al.* 1997, Srinivasan *et al.* 2002, 2003, and Nikolayev 2008). Those referenced, and many others, too, 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 begin to grow at different times during depressurization. Others have concentrated just on hypobaric depressurizations (Foster *et al.* 2000a,b, Kumar *et al.* 1992, Kumar & Powell 1994, Conkin *et al.* 1996, Pilmanis *et al.* 2004, Thompson *et al.* 2003). Recent advances in probabilistic modeling came through the use of techniques from survival analysis. Weathersby & Gerth 2002 and Tikuisis & Gerth 2003 provide additional details about probabilistic DCS modeling.

#### **4.6.2.1 Tissue Bubble Dynamics Model (TBDM)**

The TBDM is a biophysical model of bubble growth in tissue (Gernhardt 1991) that has been used in development of decompression protocols for more than 25,000 commercial dives and used by NASA in the development of EVA prebreathe protocols (Gernhardt 2008). In the model, assumed fixed values for several parameters, such as blood-tissue  $N_2$  partition coefficient, initial radius of micronuclei,  $N_2$  diffusivity between tissue and bubble, surface tension on a spherical bubble, and tissue bulk modulus are used to describe mass balance of tissue and bubble gases for a single growing bubble in a unit volume of tissue (details in Figure 2).

When inputted with the relevant durations, rates, pressures, and gas compositions the TBDM generates an output called bubble growth index (BGI), which is the time-varying ratio of bubble radius to an initial 3- $\mu\text{m}$  radius of the bubble nucleus. The BGI for a decompression exposure is calculated over the duration of the exposure with the peak BGI value typically being used as the primary measure of decompression stress. Although the TBDM accommodates modeling of multiple half-time compartments to reflect the varying rates at which different body tissues take up and eliminate inert gases, the model typically includes only a 360-minute theoretical half-time for tissue  $N_2$  kinetics when it is used to estimate decompression stress during EVAs.



$$\frac{dr}{dt} = \frac{-\frac{\alpha D}{h} \left( P_B - vt + \frac{2\gamma}{r} + \frac{4}{3}\pi r^3 M - P_t - P_{met} \right) + \frac{rv}{3}}{P_B - vt + \frac{4\gamma}{3r} + \frac{8}{3}\pi r^3 M}$$

**r** = bubble radius (cm)

**t** = time (sec)

**$\alpha$**  = Ostwald  $N_2$  solubility

(0.0125  $cm^3_{gas}/cm^3_{tissue}$  for water at 37°C)

**D** = diffusion coefficient ( $2.0 \times 10^{-8} cm^2/sec$  for water)

**h** = bubble film thickness ( $3.0 \times 10^{-4} cm$ )

**$P_B$**  = initial ambient pressure (dyne/cm<sup>2</sup>)

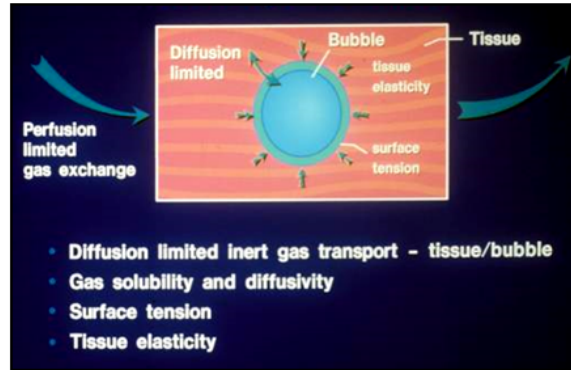
**v** = ascent or descent rate (dyne/cm<sup>2</sup>×t)

**g** = surface tension (30 dyne/cm)

**M** = tissue modulus of elasticity, the ratio of bulk modulus (H) of  $2.5 \times 10^8$  dyne/cm<sup>2</sup> to articular cartilage volume ( $H/cm^3_{tissue} = M$ , dyne/cm<sup>2</sup>×cm<sup>3</sup>) times bubble volume  $\frac{4}{3}\pi r^3$  to compute a deformation pressure (dyne/cm<sup>2</sup>)

**$P_t$**  = total tissue tension of all inert gases (dyne/cm<sup>2</sup>) in the general model but is specifically tissue  $N_2$  tension ( $P_{tis}N_2$ ) in EVA applications

**$P_{met}$**  = metabolic gas ( $O_2+CO_2+H_2O$ ) tensions ( $1.76 \times 10^5$  dyne/cm<sup>2</sup>, or 132 mmHg)



**Figure 2. Tissue Bubble Dynamic Model equation and parameters**

A statistical analysis of 6437 laboratory dives (430 DCS cases) compared predictions of the TBDM to the Workman M-value and the Hempleman PrT index, with TBDM predictions (BGI) yielding best log-Likelihood and Hosmer-Lemeshow (H-L) goodness-of-fit test (Gernhardt 1991). BGI also provided significant prediction ( $p < 0.01$ ) and goodness-of-fit for DCS (H-L  $p=.35$ ) and VGE (H-L  $p=.55$ ) data in 345 altitude decompression exposures (57 DCS cases, 16.5% DCS, 41.4% VGE) including prebreathe staged decompressions, all with exercise at altitude and including data points at 10.2, 6.0, and 4.3 psia (Abercromby *et al.* 2008, 2015).

### 4.6.3 Modeling and Operations

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 (Gernhardt 2008). 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 (Conkin *et al.* 1998). An assumption in modeling is that the outcome variable is known with certainty, which is not the case (Weathersby *et al.* 1984, Freiburger *et al.* 2004, Conkin *et al.* 2006), and adds an additional level of uncertainty to probabilistic modeling.

Table 1 shows the DCS incidence from PB protocol ground validation trials in comparison to the flight DCS incidence and the modeling predictions that take into account the operational changes from the ground trial protocol to the in-flight operational PB protocol (Conkin & Powell 2001). Accepting a new PB protocol without prior ground testing validation is rare, but the ISS campout

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protocol was accepted in 2005 based on empirical evidence and modeling analysis. It has been successfully used from ISS to support over 145 person EVAs to date.

**Table 1: Observed and model-estimated probability of DCS for NASA prebreathe protocols as of May 6, 2016.**

<b>Prebreathe Option</b>	<b>Ground Trial Subjects Tested</b>	<b>Ground Trial DCS Incidence (95% CL*)</b>	<b>Model Prediction<sup>†</sup> P(DCS) (95% CI**)</b>	<b>EVAs using PB Option</b>	<b>Flight DCS Incidence (95% CL*)</b>
4-hr In-Suit	28	21.40% (9.8-38.0%)	4.60% (2.2-9.4%)	6	0% (0.0-60.0%)
Campout	--	--	2.80% (1.2-5.9%)	146	0% (0.0-2.7%)
CEVIS	45	0% (0.0-6.5%)	2.00% (0.4-9.2%)	52	0% (0.0-9.2%)
ISLE	47	4.20% (0.7-12.8%)	0.30% (0.01-6.3% <sup>††</sup> )	40	0% No 95% CL calculated

\*From binomial distribution – one-side 95% CL

\*\*From regression models that provides 95% CI

<sup>†</sup>Model predictions include operational prebreathe margin and effects of microgravity.

<sup>††</sup>Based on option 1 operational prebreathe given nominal 6.8 ml/kg/min.

Existing models can only be extrapolated to the Exploration Atmosphere environment because the data underlying the model assumptions are based on depressurizations from 14.7 psia. An example of the application of probabilistic DCS models is provided in Table 2. The simulations for final in-suit PB times are based on an assumption of equilibrating to an atmosphere of 8.0 psia with 32% O<sub>2</sub> prior to the final in-suit PB. Even with the recent recommendation to adjust to 8.2 psia with 34% O<sub>2</sub>, the partial pressure of N<sub>2</sub> remains the same, therefore the computed P(DCS) would not change (Norcross et al. 2013).

**Table 2: Examples of model-estimated P(DCS) for Simulated Lunar Mission**

P1N <sub>2</sub>	PB (min)	TR	P(DCS) (95% CI)	P(VGE)	P(G <sub>IV</sub> VGE)	P(serious DCS)
5.57	0	1.29	0.13 (0-0.30)*	0.20	0.19	0.003
5.57	22	1.25	0.099 (0-0.26)	0.15	0.16	0.002
5.44	0	1.26	0.10 (0-0.27)	0.17	0.17	0.003
5.44	22	1.22	0.082 (0-0.21)	0.13	0.14	0.002
5.44	30	1.19	0.06 (0-0.18)	0.10	0.12	0.0017
reference			Conkin <i>et al.</i> 1996	Conkin <i>et al.</i> 1990	#	Conkin 2001

All estimates are extrapolations from statistical models.  
 Results based on 8-hr EVA with equivalent 1-G ambulation and mild exercise.  
 EVA after equilibration to 8.0 psia with 32% O<sub>2</sub>.  
 # unpublished Grade IV VGE regression from Conkin, n = 549 NASA records.

Additional analysis to supplement Table 2 is now summarized. EVAs at remote locations must maximize limited resources such as O<sub>2</sub> and also minimize DCS. The proposed exploration atmosphere PB protocol requires astronauts to live in a mildly hypoxic atmosphere (P<sub>1</sub>O<sub>2</sub> = 128 mmHg) at 8.2 psia with 34% O<sub>2</sub> while periodically performing EVAs at 4.3 psia (Abercromby *et al.* 2015). Empirical data are required to confirm that the protocol meets the current accept requirements: ≤ 15% incidence of Type I DCS, ≤ 20% incidence of Grade IV VGE, both at 95% statistical confidence, with no Type II DCS symptom during the validation trial. Our current (2015) DCS survival model (Conkin *et al.* 2014, 2015, 2015a) calculates a low probability of DCS of 1.5% (0.8 to 2.8%, 95% CL) for a 6-hr simulated EVA for physically active ambulatory subjects based on a computed tissue ratio of 1.22, a bubble growth index of 17, a body mass index of 24, and age of 32 yr, and increases to 2.3% (1.2% to 4.4%) for age 45.

## 4.7 Ground Based Chamber Study Evidence

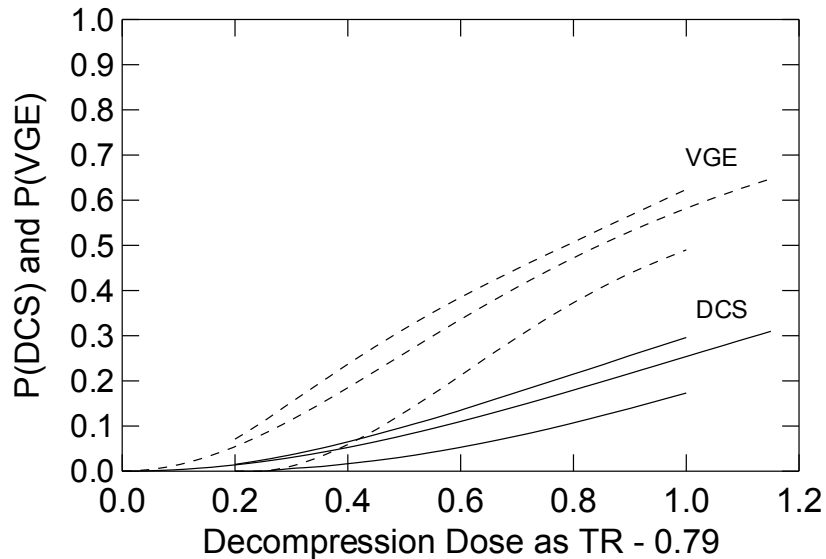
Validation testing often precedes the implementation of a PB protocol for space operations. The first test of several PB protocols was in August 1982, with DCS reported after a 3.5-hr PB in one subject and a Doppler Technician (Conkin *et al.* 1990, 2003). This was an inauspicious start to the validation of a 3.5-hr PB. A 4-hr PB reduced the incidence of DCS from 42% to 21% and reduced 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 (Waligora *et al.* 1984, Conkin *et al.* 1990). On April 12, 1981, the Shuttle STS became a reality. The first EVA from the Shuttle was on April 7, 1983, using a 3.5 hr baseline in-suit PB. Only 3 two-person EVAs have been performed

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from the Shuttle after a 3.5 or 4 hr in-suit PB since April of 1983. The 4 hr in-suit PB remained an option throughout the Shuttle program and remains an option on ISS.

The inefficiency of an in-suit PB and the possibility of a break in PB during the transition from an O<sub>2</sub> mask to the spacesuit required that NASA validate the staged 10.2 psia protocol in the early 1980's. Variations of similar protocols soon emerged, along with a desire to summarize all the results with a simple decompression dose. In addition to the DCS outcomes, routine ultrasound bubble monitoring provided an unbiased assessment of the decompression dose. The Spencer 0 – IV categorical scale (Spencer 1976, Neuman *et al.* 1976) was adopted, and the following standard 4 min evaluation scheme to improve bubble detection and grading was implemented at JSC (Adams *et al.* 1979): A Doppler technician located 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 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.

Figure 3 illustrates decompression dose-response curves for DCS and VGE outcomes from 341 exposures to 4.3 psia in altitude chambers at JSC. These subjects breathed 100% O<sub>2</sub> through a mask, and were otherwise in a comfortable shirtsleeve environment. The mean exposure time was  $4.4 \pm 1.3$  hr, and subjects ambulated from one 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.* 2003. At intervals of about 15 min, the pulmonary artery was insonated with an ultrasound 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 (Allen *et al.* 1971), and their response to repressurization (Krause & Pilmanis 2000) are as important as the overall incidence of DCS and VGE to a final decision to accept a protocol.



**Figure 3. 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 3 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 and available through their [website](#). Operational questions dictated the sequence of testing in Table 3. The first trials evaluated the 3.5 (Tests 1a and 2a) and then 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 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 found not to be a concern in repetitive hypobaric depressurizations (Cooke *et al.* 1975, Conkin *et al.* 1990, Pilmanis *et al.* 2002), so repetitive EVAs from the Shuttle was 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 where simulated suit pressure was 6.0 psia with 60% O<sub>2</sub>. A trial of an 8-hr resting PB (Test 5b) established the benefits of extreme prebreathing, even if not practical from an operational perspective. The influence of high work rate during EVA was evaluated using a row machine (Maio *et al.* 1970), a consequence 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.* 1992). The consequences of ambulation before and during an altitude exposure were evaluated at both 6.5 psia and 4.3 psia in the *Argo* series, starting with Test 9a and ending with Test 11a. Test 9a included ambulatory

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controls and Test 9b were 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 (Kumar *et al.* 1993a). Astronauts sometimes fly in commercial airliners or fly 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.

*Risk of Decompression Sickness (DCS)*

**Table 3: Summary of DCS and VGE in Tests from 1982-2015**

Test	P2 (psia)	conditions	number m 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
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 III	4.3	P,E,S,A	8 1	29.9	2!	1	1
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
Nuc-1	4.3	P,E,S	16# 5	36.4	4	13	6
Nuc-3*	4.3	P,E,S	23 7	37.0	2	9	3

Conditions: P, some PB occurred before ascent; S, a portion of the PB was spent at 10.2 psia breathing 26.5% O<sub>2</sub>; A, subjects were “adynamic” (no ambulation before or during the altitude exposure); E, a prescribed exercise was performed during some interval of the PB; FAD, flying after diving; ! One case was classified as Type II DCS; !! 2 were classified as Type II DCS; #

One case of LVGE was removed early so total count for DCS is n=20; \*as of 09/04/2015 since testing of Nuc-3 continues.

As part of the NASA Prebreathe Reduction Program (PRP), several 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  $\mu$ G (Powell *et al.* 1992, Conkin & Powell 2001, Vann & Gerth 1997, Webb *et al.* 2010), although there are contrary observations (Ballidin *et al.* 2002, Webb *et al.* 2005a). In PRP Phases I through IV, researchers evaluated the influence of combined intense dual-cycle ergometry 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, the subjects were depressurized to 10.2 psia over 30 min while still breathing 100% O<sub>2</sub>, and then 30 min were spent at 10.2 psia breathing 26.5% O<sub>2</sub> to reproduce the suit donning conditions in the ISS airlock. Then 100% O<sub>2</sub> was reintroduced into their masks and they were repressurized 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 the 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 PRP 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 none met the prospective accept conditions. The final trials in this series (Phase V-5) extended mild exercise and the total PB time to 190 min that included a 30-min suit donning step at 10.2 psia and 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.* 2003, 2004 for trials from 1a to Phase IV. Details from Phases V-1 to V-5 are in Gernhardt & Pollock 2006. At the conclusion of V-5, attention turned to the contribution of ambulation towards the incidence of DCS and VGE. All tests under the PRP imposed non-ambulation during the PB and while at 4.3 psia, our analog of lower body activity in  $\mu$ G. However, exploration class EVAs will include significant ambulation on a planetary surface, so ambulation while at 4.3 psia without ambulation during the PB, designated nucleation 1 test (Nuc-1), and ambulation during the PB without ambulation at 4.3 psia, designated nucleation 3 test (Nuc-3), were evaluated with Phase II serving as the historical control (no ambulation during PB or while at 4.3 psia). The Nuc-3 trial continues, with a preliminary summary that DCS, VGE, and Grade IV VGE are significantly greater in Nuc-1 compared to Phase II control. Conclusions related to Nuc-3 await final results (Pollock *et al.* 2015, Conkin *et al.* 2016).

#### 4.7.1 Master Logic Diagram

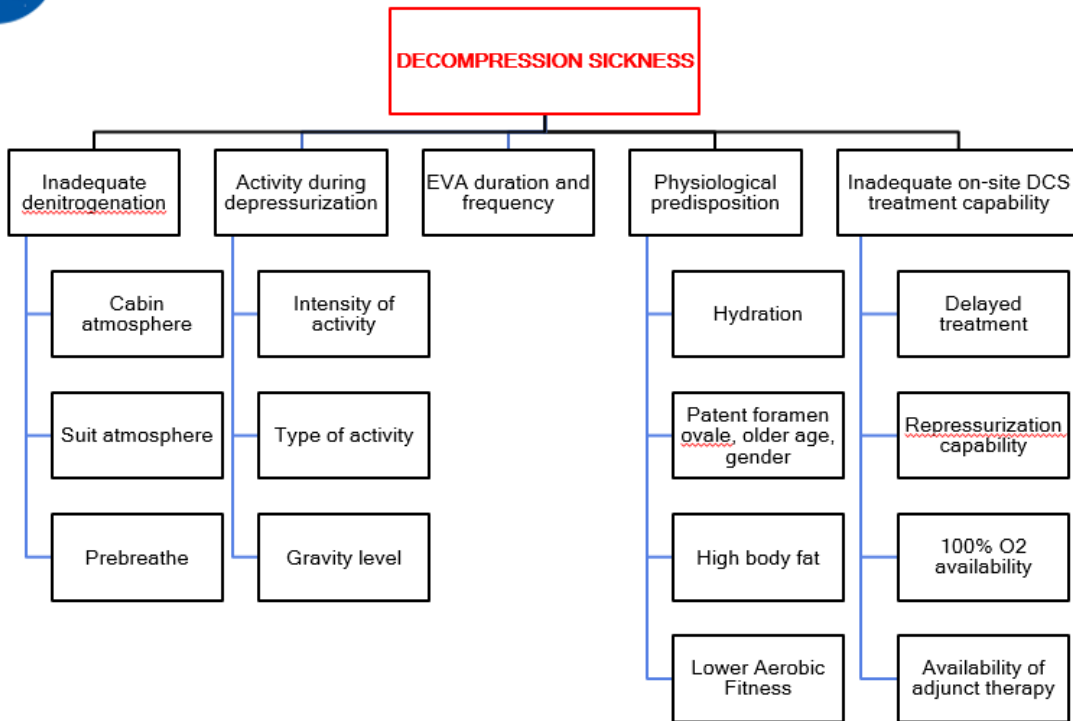
The goal of most ground based research studies was to determine if a given operational PB protocol would reduce the P(DCS) to acceptable levels. Even under this operational research paradigm, where certain risk factors for DCS were not systematically evaluated, a growing body of evidence accumulated to describe certain factors that contribute DCS. Known factors are shown in Figure 4, the Master Logic Diagram, which describes the various factors that contribute



to DCS likelihood and consequence. Understanding of these factors are a result of variations of ground based chamber studies of PB protocols intended to protect astronauts from DCS during EVA.



## Master Logic Diagram Draft



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**Figure 4. Understanding and managing DCS has many components, as seen in the Master Logic Diagram for DCS.**

### 4.7.2 Inadequate Denitrogenation

Much about denitrogenation and hypobaric DCS that was learned during and shortly after WW II is available on the pages of Fulton’s 1951 book (Bateman 1951, Jones 1951), with additional information in the 4<sup>th</sup> edition of *Fundamentals of Aerospace Medicine* (Stepanek & Webb 2008) and from *The Proceedings of the 1990 Hypobaric Decompression Sickness Workshop* (Pilmanis 1992). The advent of Doppler ultrasound bubble detection technology in the 1970s provided a significant tool to understand 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, which typically uses oxygen (O<sub>2</sub>)

prebreathing, an astronaut has a small amount of tissue nitrogen ( $N_2$ ) to manage. Once the astronaut depressurizes to a low-pressure spacesuit, the volume expansion (Boyle's Law) of this remaining  $N_2$  at the new lower pressure is concerning.

One major contribution to how much  $N_2$  stays in the body after a PB is body fat content. It is important to define the minimum PB time that protects the greatest number of EVA astronauts, be they 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 (McIver *et al.* 1967). Risk is defined as the P(DCS) and the consequence of DCS, and since the consequence of a serious case of DCS in space is high, then the P(Serious DCS) must be very low to achieve an acceptable operational risk.

Males and females each display a wide range of body types. A brief generic comparison using gender illustrates that no two people have the same quality or quantity of  $N_2$  elimination (washout) and uptake (washin). Table 4 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 the man, given an  $N_2$  solubility coefficient of 0.0146 ml (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 4: 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 g/mL, Density of lean tissue = 1.1 g/mL, 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.

Apparent in this example is that the amount of  $N_2$  in fat tissues of the woman is twice that of 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 the man and the woman. But PB time is always limited, so 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. In this example, a large amount of  $N_2$  would quickly be eliminated from the well-perfused and large lean tissue reservoir in the male, with a lesser amount of  $N_2$  coming from the poorly perfused fat depot that is smaller than that in the woman. The poorly perfused fat contributes some  $N_2$  throughout the PB, but is likely responsible for the long tail of a typical  $N_2$  elimination curve. The female also provides a large amount of  $N_2$  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. The 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 one for men.

It is important to define the minimum PB time that protects the greatest number of EVA astronauts, be they 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 (McIver *et al.* 1967). Risk is defined as the P(DCS) and the consequence of DCS, and since the consequence of a serious case of DCS in space is high, then the P(Serious DCS) must be very low to achieve an acceptable operational risk.

#### **4.7.2.1 Air Break during Prebreathe**

Various methods to preserve the quality of and confidence in the PB during the transition from the mask to the 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 ISS (Horrigan & Waligora 1980, Powell *et al.* 1994a). The few research studies that exist about break in PB are listed here in chronological order: Clarke *et al.* 1945, Bateman 1951, Cooke 1976, Adams *et al.* 1977, Horrigan *et al.* 1979, Dixon *et al.* 1980, Barer *et al.* 1983, and the most recent Pilmanis *et al.* 2010.

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 define O<sub>2</sub> payback time based on the location and duration of a simple air break during a PB. Payback time is the number of min 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<sub>2</sub> is 2 times the duration of the air break, and 4 times the duration if the air break occurs early in the Exercise PB protocol for the ISS. A break in PB longer than 10 min requires that the PB be repeated from the start, or that the crew switch to an alternative PB. A notable case of a complicated break in PB occurred during the 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 repressurization 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 (Cooke 1976) to 35 times (Adams *et al.* 1977) 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 two people have identical N<sub>2</sub> 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 are infinitely variable. Breathing 1 ATA of O<sub>2</sub> is known to decrease cardiac output and to increase peripheral vascular resistance by increasing vasoconstriction (Andersen & Hillestad 1970, Anderson *et al.* 1991). It is reasonable to suppose asymmetrical N<sub>2</sub> 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<sub>2</sub> window during the PB (Van Liew *et al.* 1993), and the size distribution is influenced by air breaks. So simple payback rules may not suffice under all conditions, and a quantitative approach to assess

payback time is a goal for the future (Conkin 2011). Data from Pilmanis *et al.* 2010 showed that a 10 min air break 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.

#### **4.7.2.2 Hypobaric Ascent Limit**

The need for high-altitude bombing during WW II 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 (Fulton 1951, Adler 1964, Fryer & Roxburgh 1965). It was quickly realized that the altitude attained, the 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 (Conkin 2001, Conkin *et al.* 2002). 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<sub>2</sub> mixtures dramatically reduced both pain-only and serious DCS, and most fit young men could tolerate a degree of depressurization even without the benefit of a PB. During the war years, the 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 6,096 and 7,620 m (20,000 and 25,000 ft) were acceptable in most operational settings. Several studies were initiated to identify and then screen out personnel who were potential “weak links” as a means to reduce the impact of DCS on the mission. These efforts were abandoned as ineffective and costly, but highlighted the reality of between and within subject variability to DCS. As the interest in aviator DCS increased after WW II, primarily through the United States Air Force (USAF) and NASA, a systematic approach led to a better understanding of hypobaric ascent limit. Also, a shift in thinking from “tolerable” symptoms to the first onset of mild symptoms reduced the threshold altitude for DCS.

Each year, millions of people on commercial flights are quickly exposed to between 1,829 and 2,438 m (6,000 and 8,000 ft) altitude for long periods. Most barophysicists would agree that a rapid ascent to 3048 m (10,000 ft) is without significant risk of DCS, but hypoxia soon limits useful physical activity. The use of enriched O<sub>2</sub> at higher altitudes confounds the basic question about the DCS limit to direct ascent on air (Webb & Pilmanis 1993). 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, and a spacesuit pressurized greater than the lowest pressure to cause venous gas emboli (VGE) and DCS could be an option to eliminate the risk of DCS (Flugel *et al.* 1984).

Work to define the threshold for a no PB spacesuit suggests that 4,420 m (14,500 ft) altitude is close to a no-DCS ascent, with VGE still produced at an altitude of 3,505 m (11,500 ft) (Conkin *et al.* 1990). Webb *et al.* 1989 showed that a spacesuit at 9.5 psia (11,500 ft) prevented DCS during 5 repeated exposure in 22 subjects. 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.

*Risk of Decompression Sickness (DCS)*

Table 5, modified from Conkin *et al.* 1990, lists hypobaric exposure pressures and the associated DCS and VGE incidence.

**Table 5: Tests to Find Threshold Altitudes for DCS and VGE**

<b>P1N<sub>2</sub> / P2</b>	<b>P2 (psia)</b>	<b>DCS cases / n</b>	<b>VGE cases / n</b>	<b>reference</b>
1.49, day 1 of 3	7.8	2 / 64 = 3.0%	28 / 64 = 43%	Dixon 1986,1988 Conkin 1990
1.43, day 2 of 3	7.8	2 / 62 = 3.0%	29 / 62 = 46%	Dixon 1986,1988 Conkin 1990
1.42, day 3 of 3	7.8	1 / 60 = 1.6%	25 / 60 = 41%	Dixon 1986,1988 Conkin 1990
1.40	8.3	1 / 31 = 3.2%	8 / 31 = 26%	Webb 1988, Smead 1986,
1.36	8.5	0 / 9 = 0%	3 / 9 = 33%	USAF pilot study* Conkin 1990
1.29	9.0	0 / 16 = 0%	7 / 16 = 43%	USAF pilot study* Conkin 1990
1.22	9.5	0 / 6 = 0%	1 / 6 = 17%	USAF pilot study* Conkin 1990
1.22	9.5	0 / 31 = 0%	8 / 31 = 26%	USAF pilot study* Conkin 1990
1.22, day 1 of 5	9.5	0 / 23 = 0%	0 / 23 = 0%	Webb 1989, Dixon 1985, Conkin 1990
1.11, day 2 of 5	9.5	0 / 22 = 0%	0 / 22 = 0%	Webb 1989, Dixon 1985, Conkin 1990
1.10, day 3 of 5	9.5	0 / 22 = 0%	0 / 22 = 0%	Webb 1989, Dixon 1985, Conkin 1990
1.10, day 4 of 5	9.5	0 / 22 = 0%	0 / 22 = 0%	Webb 1989, Dixon 1985, Conkin 1990
1.10, day 5 of 5	9.5	0 / 22 = 0%	0 / 22 = 0%	Webb 1989, Dixon 1985, Conkin 1990
1.16	10.0	0 / 8 = 0%	2 / 8 = 25%	USAF pilot study* Conkin 1990

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

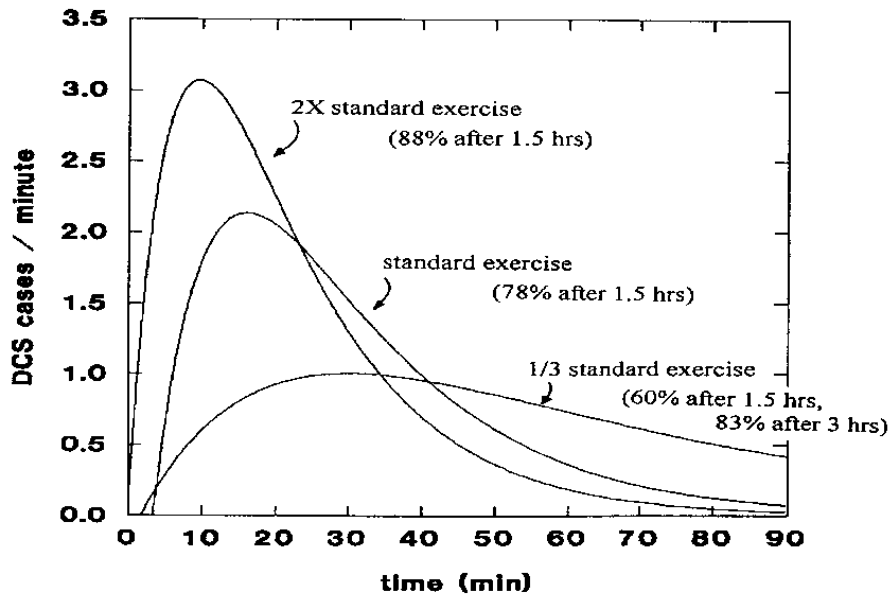
Kumar *et al.* 1990 and Webb *et al.* 1998 summarized the information in Table 5 and other information about altitude threshold, but came to different conclusions. Kumar stressed that any threshold for symptoms is conditional on other factors, with his lowest conditional threshold defined as 3,353 m (11,000 ft) altitude. Webb reported about 5% DCS for 6,096 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 (Rudge 1990b, Voge 1989).

#### 4.7.3 Activity during EVA

No single variable, other than O<sub>2</sub> PB time, has more of an impact on the P(DCS) than exercise at altitude. Cook (1951) summarizes the importance of exercise at altitude as a factor to increase

the incidence, the severity, and shorten the latency time to the first report of DCS. One can limit the P(DCS) at a given suit pressure by limiting exercise during EVA, but this is impractical in most applications since astronauts are performing physical tasks during an EVA. The general approach is to provide sufficient PB so that the type, intensity, and duration of EVA work are not considerations. Ambulation that stresses the knees and ankles on the surface of the moon or Mars is expected to increase the risk of DCS for any PB protocol that otherwise performed well in  $\mu\text{G}$  (Conkin *et al.* 1987, Conkin *et al.* 2001, Webb *et al.* 2010).

Figure 5 is a classic presentation of the importance of exercise type and intensity toward the P(DCS). The figure is redrawn from Henry (1956). It shows the rate of DCS as a function of lower body exercise intensity during a stair-step challenge.



**Figure 5. The rate of DCS as a result of exercise after an ascent to 3.0 psia without PB. Standard exercise was 10 step-ups on a nine inch stool in 30 sec, repeated at 5 min intervals.**

#### 4.7.4 Exercise Effects on Micronuclei

The previous discussion focused on reducing the amount of tissue  $\text{N}_2$  to limit bubble growth, the classic Haldanean approach, but an emerging area of DCS prevention is to also hinder the transformation of tissue micronuclei into growing bubbles (Tikuisis & Gerth 2003, Blatteau *et al.* 2006). The presence of gaseous micronuclei in the tissues permits DCS under modest depressurizations (Weathersby *et al.* 1982). Information about and evidence for tissue micronuclei come mostly from indirect observations. One consistent inference from these studies is that normal activity establishes a size distribution of micronuclei within tissues, which can then be modified by changing the type, timing and intensity of activity.

If micronuclei are considered and if the results from research on DCS are then applied to astronauts who perform EVAs, then walking in an altitude chamber is not a reasonable analog to

EVA or “space walking” (Powell *et al.* 1992, Powell *et al.* 1993, Vann & Gerth 1997). Exercise during depressurization increases the risk of DCS, generally in the limb performing the exercise (Conkin *et al.* 1987, Cooke 1951, Henry 1956, Krutz & Dixon 1987). 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 and when they ambulate on the Moon and later Mars, especially as it relates to the risk of DCS. Calling an EVA in  $\mu\text{G}$  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 that the upper body can effect some task. Powell coined the term “adynamia” to characterize the lack of movement and, therefore, the lack of dynamic forces in the lower body (lower body adynamia) over several days of adaptation to  $\mu\text{G}$  and during EVAs (Powell *et al.* 1994, 1995, Kumar *et al.* 1993a, Conkin & Powell 2001).

The fundamental premise of adynamia is about 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. However, the number or distribution of micronucleus sizes can be influenced 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 the ergometry about 15 min into the start of the PB (Conkin *et al.* 2004). 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 that use the Exercise PB protocol start the PB at the same time, but someone must go first since there is only one leg ergometer on the ISS dedicated to this protocol.

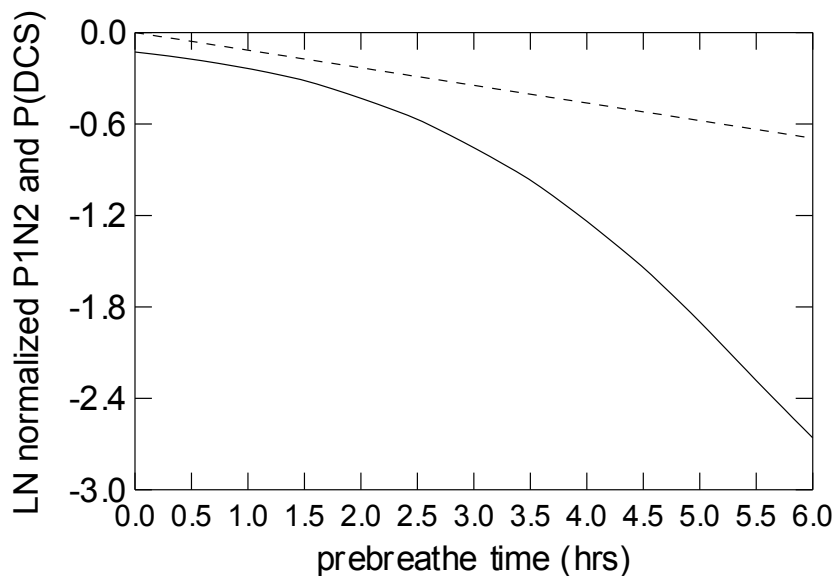
Violent muscular contractions in bullfrogs before a hypobaric exposure (Whitaker *et al.* 1945) were associated with bubble formation in the resting animals while at altitude. The number of bubbles was reduced if the frogs were allowed to recover for as long as 1 hr after electrical stimulations. The authors offered 2 explanations: a short-lived local increase in carbon dioxide ( $\text{CO}_2$ ) 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 same concept was tested in humans (Dervay *et al.* 2002) 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 did 150 deep knee flexes in 10 min either 2 hr, 1 hr, or just before 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  $\text{CO}_2$ ) 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 them 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  $\text{N}_2$  supersaturation, then perhaps the decrease in  $P(\text{DCS})$  tracks the decrease in computed supersaturation. If the relationship is not a mirror image, then



perhaps factors other than  $N_2$  supersaturation are co-responsible. The dashed line in Fig. 3 is from the natural logarithm transformation of the exponential decay in a 360 min half-time compartment normalized by dividing the initial tissue  $N_2$  pressure by 11.6 psia, ambient  $pN_2$  at sea level. The solid curve is the same transformation applied to the P(DCS) from a survival model (Conkin *et al.* 1996) 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 the potential for evolved gas and the transformation of micronuclei into bubbles, then it might be expected that the curves for  $\log[P(\text{DCS})]$  and  $\log(\text{normalized } N_2 \text{ pressure})$  would diverge over a range of PB time.

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 (Van Liew & Raychaudhuri 1997, Van Liew 1998, Van Liew & Conkin 2007). 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 where fewer and smaller-radius micronuclei exist to subsequently transform into growing bubbles under the prevailing reduced  $N_2$  supersaturation, as suggested by the rapid decrease in  $\ln[P(\text{DCS})]$  after 3 hr of PB in the survival model (Figure 6). 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 it 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.



**Figure 6. Change in computed tissue  $N_2$  pressure (dashed curve) and the P(DCS) (solid curve) as a function of PB time, under conditions of the simulation described in text.**

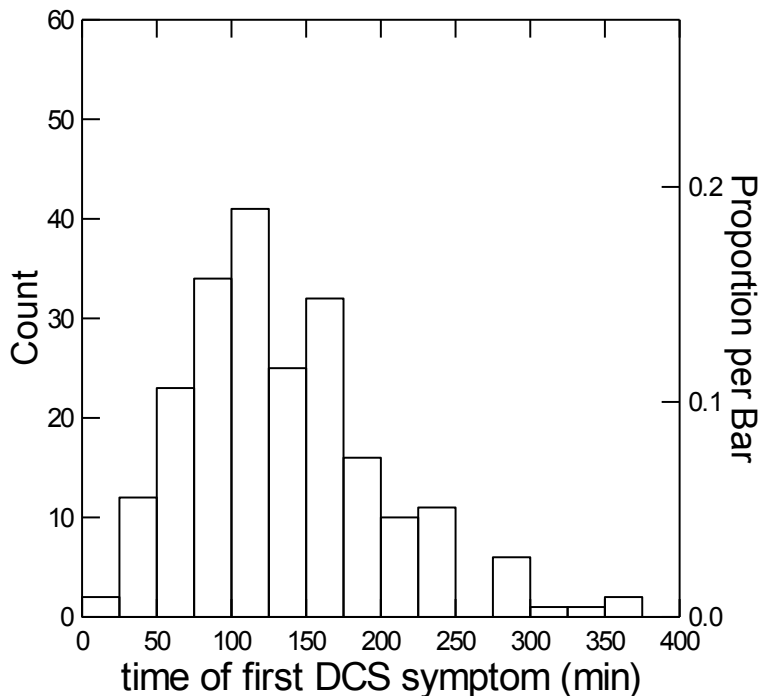
The classic soda-bottle analogy of bubbles in the body illustrates the physical consequence of depressurization, but emerging science suggests that activation of various stress-induced biomolecules before, during, or after depressurization will influence the DCS and VGE outcomes

(Dujic *et al.* 2006, Valic *et al.* 2007). Astronauts routinely take aspirin and other pharmacological agents to manage the stress and discomforts of space flight and EVAs, which may influence the DCS and VGE outcomes. 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 (Wisloff *et al.* 2004).

#### 4.7.5 Duration and Frequency of EVA

The evolution of gas in tissue is a time-dependent process. Nims (1951) systematically describes the time-dependent process in the development of his theoretical model to describe aviator DCS. Gas evolution has a lag phase, a growth phase, and finally a recovery phase if the EVA continues since tissue and bubble N<sub>2</sub> continues to be removed while breathing 100% O<sub>2</sub> during the EVA. One can limit the P(DCS) at a given suit pressure by limiting the EVA exposure time, but this is impractical in most applications. The general approach is to provide sufficient PB so that EVA duration is not a consideration.

Figure 7 shows the distribution of symptom failure times from denitrogenation protocols that are considered conservative, based on NASA PB validations. Symptom failure times are most likely 75 to 175 min in these data, with fewer cases appearing in minutes and other at 6 hrs. There is a period during any EVA, about 3 hrs, after which the likelihood is small that DCS will be reported. Again, this is attributed to the continued removal of N<sub>2</sub> during the course of an EVA.



**Figure 7. Histogram distribution of time in 216 symptoms in 119 cases of DCS. Distribution is skewed right with largest number of reports at about 120 min into the exposures.**

Although EVA has historically been a single event in a flight day, that may not be the standard operational concept for future exploration missions. Development of the Exploration Atmosphere in combination with the use of suitports will allow for the possibility of multiple EVAs in a single day or at a minimum, the ability to perform EVAs multiple days in a row. Currently, exploration design reference missions assume that all crewmembers are capable of performing up to 24 hours of EVA per week. EVAs have historically been treated as a single isolated event in relation to management of DCS risk, but this will no longer be the case. Most evidence supports the idea that the use of frequent, shorter EVAs with intermittent recompression is likely to decrease overall DCS risk, but empirical testing followed by flight experience would be the preferred evidence base (Abercromby *et al.* 2015, Abercromby *et al.* 2008, Mollerlokken *et al.* 2007, Pilmans *et al.* 2002.)

#### 4.7.6 Physiological Predisposition and Risk of DCS

It has been observed that some divers and aviators are particularly resistant or susceptible to DCS and VGE (Weathersby 1989, Kumar *et al.* 1992, Webb *et al.* 2005). Depressurization schedules developed to protect the most susceptible are then ultra-safe for the resistant, and therefore not very efficient. So, there 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 (Allen *et al.* 1971). 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.

Table 6 lists examples of factors associated with risk of DCS and the associated references. Any global conclusions on individual factors are confounded by inconsistencies in the DCS mitigation strategy (primarily PB duration) and decompression dose and duration. Law and Watkins (2010) reviewed literature on individual susceptibility to DCS, but provided no additional recommendations for astronaut screening and did not refute the current practice of eliminating astronaut candidates due a flow-significant atrial septal defects.

**Table 6: Individual Factors Associated with Risk of DCS and VGE**

Factor Associated with Risk of DCS and VGE	Some Reference(s)
Age	Conkin <i>et al.</i> 2003, Eckenhoff <i>et al.</i> 1990, Cameron <i>et al.</i> 2007, Sulaiman <i>et al.</i> 1997, Carturan <i>et al.</i> 2002, Schellart <i>et al.</i> 2012
PFO	Saary & Gray 2001, Foster <i>et al.</i> 2003
Gender	Webb <i>et al.</i> 2003, Conkin 2010, Thompson <i>et al.</i> 2003, Vann <i>et al.</i> 1993
Menstrual Cycle Time	Rudge 1990a, Webb <i>et al.</i> 2003
Aerobic Fitness	Dujić <i>et al.</i> 2004, 2008, Carturan <i>et al.</i> 1999, Webb <i>et al.</i> 2003, Webb <i>et al.</i> 2005
Body Fat	Webb <i>et al.</i> 2003, Webb <i>et al.</i> 2005
Hydration Status	Fahlman & Dromsky 2006

One challenge in understanding the contribution of these factors to DCS and VGE outcomes is that all are 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 (Kumar *et al.* 1993).

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 (Conkin 1994, Kumar & Powell 1994). Although a 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, in general, this approach has not been used, and contributes to contradiction and confusion in the literature.

With limited objective data to support specific recommendations for astronaut selection and preparation, we are left with suggesting that an astronaut should be adequately hydrated prior to EVA and that increased aerobic fitness and lower body fat levels may contribute slightly to decreased DCS risk.

## **4.8 Decompression Stress**

DCS is a clinically diagnosed disorder based primarily on self-reported symptoms such as joint pain or paresthesia, therefore; one could mistakenly assume that avoiding clinical DCS is the only concern during a decompression exposure. In many cases, evolved gas bubbles do not accumulate in a joint or tissue in sufficient quantity to cause clinical DCS, yet these “silent bubbles” can be present in large quantities providing clear evidence of decompression stress in the human body. This section will describe the tenuous relationship between VGE detected in the pulmonary artery and hypobaric DCS and provide additional topics of concern related to decompression stress.

### **4.8.1 Relationship between VGE and Hypobaric DCS**

Ever since silent bubbles were 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 (Nishi 1993). 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 two are correlative as opposed to cause-and-effect. Correlative relationships differ from one study to the next depending on many factors: such as the decompression dose and the type of breathing gas (Webb & Pilmanis 1993, Pilmanis *et al.* 2003); the type of ultrasound equipment, training of the Doppler technician, and the methods used to quantify the Doppler signals, [e.g. simple bubble grades or more sophisticated “time-intensity” approaches] (Eftedal *et al.* 2007). However, the absence of VGE is strongly associated with the absence of DCS.

## Risk of Decompression Sickness (DCS)

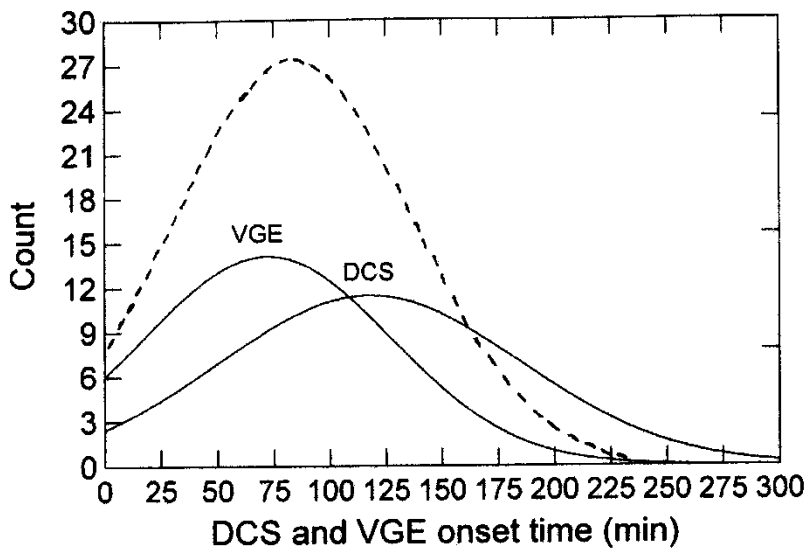
The positive and negative predictive values of VGE have been explored in both divers and aviators (Nishi 1993, Kumar *et al.* 1992a, Kumar & Waligora 1995, Conkin *et al.* 1998). The desire to have a single global understanding about the relationship between VGE and DCS is frustrated because of differences in bubbles between divers and aviators, and even differences attributed to gender (Conkin 2010). 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. But Grade IV VGE are routinely assigned in hypobaric depressurizations, even after conservative PBs (Webb *et al.* 2002). 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 (Balldin *et al.* 2004). Divers returning to 1 ATA from a provocative SCUBA dive may produce many small bubbles, predominately composed of N<sub>2</sub>. In contrast, aviators may produce fewer large bubbles composed of as much as 70% metabolic gases (Van Liew & Burkard 1994, 1995, Van Liew *et al.* 1993). Since the gas composition of VGE in divers and aviators is different, then it is reasonable to expect that the association between VGE and DCS reflect this difference. In summary, a global understanding about the relationship between VGE and DCS is not yet available. The absence of this understanding 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 where a sign or symptom may appear. Table 7 shows that the positive predictive value for DCS of any VGE grade or of Grade III and IV is only 32 or 39% (Conkin *et al.* 1996a). 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 (Olson *et al.* 1988, Balldin *et al.* 2002, Webb & Pilmanis 2011). 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 (Kumar *et al.* 1997).

**Table 7: Measures of Association Between VGE and DCS**

<b>measure</b>	<b>Grades 0 – IV (n = 1,322)</b>	<b>Grades 0, III, IV (n = 1,210)</b>
sensitivity	0.922	0.917
specificity	0.718	0.787
+ predictive value	0.323	0.391
- predictive value	0.980	0.980

Even though a one-to-one cause-and-effect relationship between VGE and DCS does not exist, there is a consistent temporal association between VGE and DCS. Figure 8 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.



**Figure 8. Time of VGE and DCS onset in 78 exposures with both present (solid curve) and 150 exposures with VGE only (dashed curve). The curves, all of which are skewed to the right, are the best-imposed normal distributions on histograms.**

The NASA Hypobaric Decompression Sickness Database contains 78 subjects with DCS onset times associated with 78 VGE onset times, with a mean TR of  $1.67 \pm 0.15$  SD. Mean DCS onset time was  $120 \text{ min} \pm 71 \text{ min SD}$  and mean VGE onset time was  $72 \pm 55$ . 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  $90 \pm 65 \text{ min}$  and mean TR of  $1.65 \pm 0.19$ . The mean VGE onset time for all 228 exposures with VGE was  $84 \pm 62 \text{ min}$ . Only 4 subjects had DCS without VGE being detected. The majority of exposures, a total of 317 out of 549 (57.7%), 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 they 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 (Conkin *et al.* 1996a, 1998).

It is appropriate here to speculate on why VGE 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 of the 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 the 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 to visualize the transport of excess N<sub>2</sub> 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.

It is preferable from a DCS standpoint to not have circulating VGE, with or without a PFO. Blood is a complex fluid and the blood-endothelial interface forms a complex homeostatic surface, so the presence of bubbles in blood and at the blood-endothelial interface could be problematic. Aviators and astronauts share one feature with divers, healthy lungs that provide an efficient filter for VGE (Diesel *et al.* 2002). But aviators and astronauts are not immune from the consequences of embolic overload, even in healthy lungs. Many factors in the aerospace environment compromise healthy lung function. These factors combined with too many bubbles entering the pulmonary circulation can put this group at high risk (Balldin *et al.* 2002). Beyond the lungs, circulating emboli may also impact other areas of the body which are well perfused. The following describes a few topics of interest that are present due to decompression stress even without symptoms of clinical DCS.

#### **4.8.1.1 In-suit Doppler Effort**

Monitoring for VGE in the pulmonary artery as the entire right-heart cardiac output enters the pulmonary circulation is the simplest approach for 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-1970's to where small, battery operated devices were safe to use in operational settings. Investigators at Brooks AFB in the early 1980'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. The idea was valid and the rewards were great, so 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 in the *Orlan* suit during altitude chamber flights.

The ability to acquire a stable, quality blood flow signal was verified during brief periods of  $\mu$ G during parabolic flight. The viscera within the chest stabilized in  $\mu$ G which allowed for good signal quality even under modest body motion (Hadley *et al.* 1984). 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 the 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 the ultrasound coupling between the sensor and skin were needed since one hour 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 (Acock *et al.* 2004, Gernhardt *et al.* 2005). This was significant since astronauts are encouraged to drink water from a 32 ounce drink bag within the EMU during long EVAs. The Doppler device, training, and use of the device under real world conditions was successful.

In spite of a successful research and development program for an automated in-suit bubble detector a final operational system did not materialize. Safety concerns about the battery-operated device within the 100% O<sub>2</sub> EMU environment halted the effort, and also prevented exposure of an astronaut to 4.3 psia while 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.

#### 4.8.2 White Matter Hyperintensities

An emerging area of interest and concern has been the increased prevalence of white matter hyperintensities (WMH) associated with occupational hypobaric exposure, particularly in the U-2 community (McGuire *et al.* 2012). Magnetic Resonance Imaging (MRI) after signs and symptoms associated with neurological DCS in some U-2 pilots shows a significant increase in counts and volume of WMH lesions compared to comparable cohorts that had no history of hypobaric exposures (Jersey *et al.* 2013, McGuire *et al.* 2013). The presence of these lesions is associated with mild cognitive deficit (McGuire *et al.* 2014, Wood & McGuire 2015). Two basic assumptions of the risk of DCS during EVA at NASA have been: 1) Lack of DCS symptoms implies no DCS has occurred, equating to a successful EVA; and 2) successful EVAs are independent of one another with no cumulative effects of hypobaric exposures; therefore, past successful EVAs have no impact on future hypobaric exposures. Sufficient evidence has recently emerged to question these assumptions. Hypobaric exposure is often associated with high incidence of VGE even when overt symptoms of DCS are not reported, indicating a subclinical decompression stress upon the body. The lack of clinical DCS symptoms continues to be equated with the absence of DCS. But recent reports involving high-altitude pilots and hypobaric chamber occupants have revealed a direct correlation between occupational hypobaric exposure and both the volume and number of subcortical WMH on MRI imaging in asymptomatic and symptomatic individuals alike.

Experts in neurology and radiology are characterizing these lesions, trying to establish a causal relationship to hypobaric exposures, such as microembolization (Weenink *et al.* 2012, Webb & Pilmanis 2011) or acute hypoxia, as well as consulting with the USAF to reverse this trend by extending rest periods between hypobaric exposures, improving denitrogenation protocols (Webb *et al.* 2010a), and providing greater pressurization in the U-2 cabin (Pilmanis *et al.* 2014). As a consequence of several recent publications, investigators at NASA-JSC in collaboration with civilian consultants from the USAF have surveyed MRI scans from astronauts. Preliminary results show more WMH lesions than expected but not enough data is available to describe



potential mechanisms or link these results to hypobaric exposure (Sherman & McGuire 2015). Collaborations continue to understand the causes, consequences, and eventual mitigation of WMH in astronauts. As a minimum, MRI surveillance of those that experience occupational hypobaric depressurizations may be warranted.

#### 4.8.3 Microparticles

A potentially related topic to WMH is recent research on circulating microparticles (MP) (Carraway & Key 2011). Processing cellular debris from different sources is part of normal human physiology. For example, the spleen clears damaged and aged erythrocytes. The majority of MP are derived from circulating cells such as platelets, leukocytes, erythrocytes, as well as vascular endothelial cells. Recent work (Thom *et al.* 2011, 2012, 2013, 2013a, 2015) has suggested that an increase in circulating MP may be a cause or consequence of inadequate depressurization, particularly in divers. They conclude that MP production and neutrophil activation exhibit strong associations with DCS symptoms. At present, only one study with preliminary results is available for hypobaric depressurization. A conclusion, at present, is that MP are not the cause or consequence of VGE, regardless of VGE intensity, in this preliminary study with low hypobaric decompression stress in contrast to much higher hyperbaric decompression stress (Pollock *et al.* 2015).

#### 4.8.4 Dysbaric Osteonecrosis

Bone is living tissue, constantly being resculpted and repaired through life. Healthy bone is subject to damage when blood flow is compromised by gaseous or solid emboli. A comprehensive review of dysbaric osteonecrosis (DO) is not provided here, but several recent reviews are available (Lehner *et al.* 1997, Jones *et al.* 1993, Chryssanthou 1978, Sharareh & Schwarzkopf 2015, Hutter 2000), and books on diving medicine always provide a chapter on DO (McCallum & Harrison, 1993, Edmonds *et al.* 1981, Walder 1976). These sources generally implicate compromised blood circulation in the unique vascular structure of bone. Differences in the distribution of white versus red marrow and the likelihood of liberating gas emboli within the marrow is given as a clue to the distribution of DO within the skeleton. But the exact pathogenesis is unknown. DO is described as “delayed” DCS since the arthritic symptoms appear much later than the decompression insult. Bone necrosis in a sheep model (Lehner *et al.* 1997) was attributed to transient ischemia after multiple stressful hyperbaric exposures resulting in DCS in all sheep after all exposures. They concluded, “DO appears to involve a bone compartment syndrome of elevated intramedullary pressure initiated by decompression induced N<sub>2</sub> bubble formation in the fatty marrow of the long bones.” One curious observation is the total sparing of the knee joint as a site of DO (Hutter 2000). Other non-gaseous emboli secondary to evolved gas are also implicated as the source of ischemia, necrosis, and bone death (Jones *et al.* 1993).

The prevalence of DO in divers, caisson workers, saturation divers, and aviators is not yet established for rigorous comparison across occupations. There is an absence of data and discussion about DO in texts on aviation medicine relative to texts on diving medicine. One reference to hypobaric bone lesions was found in our limited literature review (Hodgson *et al.* 1968), concluding bone lesions are possible but rare particularly if denitrogenation precedes the ascent. However, it can be assumed that the greater prevalence in diving than in aviation is

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because decompression stress in the diver is greater than the aviator, in general. The diver has a greater potential to embolize marrow and for a longer period than the aviator. An asymptomatic diver with silent bubbles is supersaturated with inert gas for a longer period than the aviator. A hypobaric exposure for the aviator is self-limiting; a significant Boyle's law compression of any gas phase is realized since the aviator must soon return to site pressure. The diver, on the other hand, is at low-pressure at the surface relative to the diving depth and bubbles formed during the repressurization to site pressure can persist for days. Since aviators and astronauts are not immune from silent bubbles, there is the chance that any bone damage from gaseous or solid emboli exceeds the ability to repair and restore bone circulation. This is certainly true if there are other factors to consider in bone homeostasis for astronauts undergoing adaptation to microgravity. Much has been published about changes in bone structure during acute and chronic exposure to microgravity, with some sources provided here (Buckey 2006, Schneider *et al.* 1989, Orwell *et al.* 2013, Sibonga *et al.* 2015). Fractures and repair of fractures at remote sites with greater EVA frequency is an on-going area of research. Monitoring bone health and approaches to mitigate detrimental change in bone structure is outside the scope of the DCS Evidence Report. It is clear; however, that experts on bone health and the diagnosis and treatment of DO need to be integrated into overall astronaut health and performance in exploration missions with high EVA frequency.

## **5 DCS Treatment Experience**

The many signs and symptoms as a consequence of evolved gas and a review of treatment options for those afflicted are briefly described using data from NASA. The reader is also referred to Norfleet 2008, Stepanek & Webb 2008a, Balldin *et al.* 2004, Ryles & Pilmanis 1996, Krause & Pilmanis 2000, Muehlberger *et al.* 2004, Conkin *et al.* 2003, and Jersey *et al.* 2010 for descriptions of what aviators and astronauts need to avoid to stay healthy and productive, and treatment options if evolved gas is not prevented.

A PB protocol selected for EVAs in future Exploration Class missions will be conservative. But even conservative PB protocols come with some risk. What should mission managers expect as far as the prevalence and character of symptoms? How effective is a return to habitat pressure after the EVA to resolve symptoms? What percentage of symptoms that resolves before a return to site pressure reoccurs and initiates a hyperbaric O<sub>2</sub> (HBO) treatment? These and other questions are addressed by discussing the 220 symptoms associated with the 119 cases of DCS that have accrued during hypobaric chamber studies conducted by NASA. Conkin *et al.* 2003 discussed 103 of these cases in detail from 1982-1999. These and more recent DCS cases have been analyzed with intent to develop a DCS treatment model (Conkin *et al.* 2013, 2014, 2015). Also, the effectiveness of treating symptoms at the conclusion of an EVA is described using a bubble model.

Figure 9 shows the number of Type I symptoms associated with an approximate anatomical location. The knees and ankles contribute 139 occurrences (68%) out of 203 Type I symptom occurrences. These data reflect results where subjects were ambulatory before and during the altitude exposure, but even subjects that were not ambulatory (adynamic) before and during the exposure had pain-only symptoms predominantly in the lower body. Clearly, the lower body (feet, ankles, knees) is a primary location for DCS symptoms and is not expected to change for astronauts that ambulate on the surface of Mars or the Moon.

Figure 10 shows the number of Type I symptom attributes. Pain as a symptom attribute that was constant in nature dominates how Type I symptoms were described by subjects.

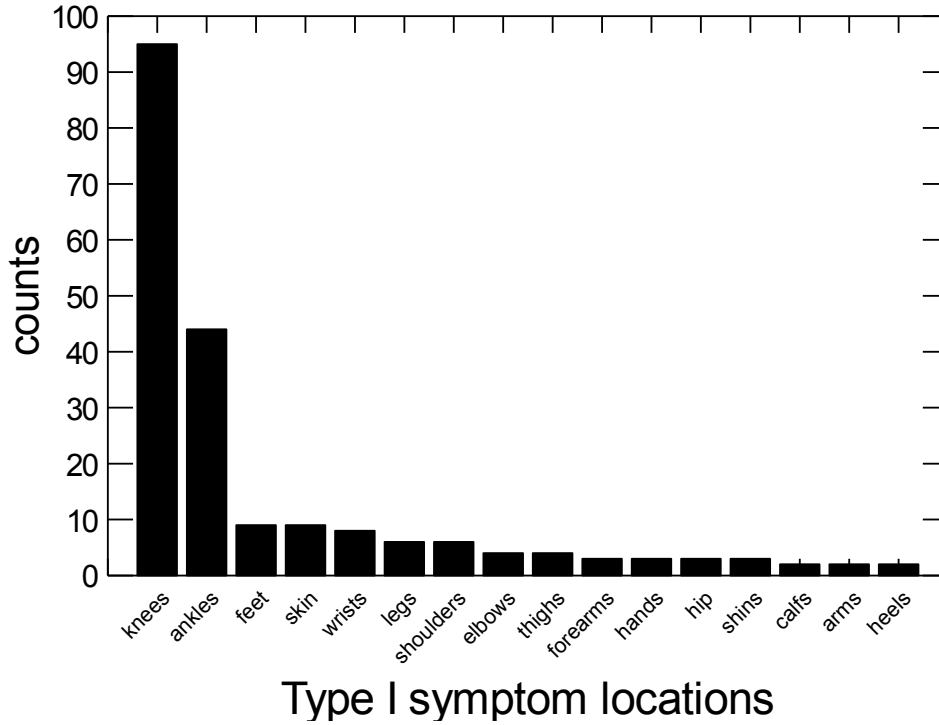


Figure 9. Number of Type I symptom occurrences in 119 cases of DCS. Symptoms in toes or fingers were included in feet or hands. One subject has skin symptoms (tingling) located in 7 body locations.

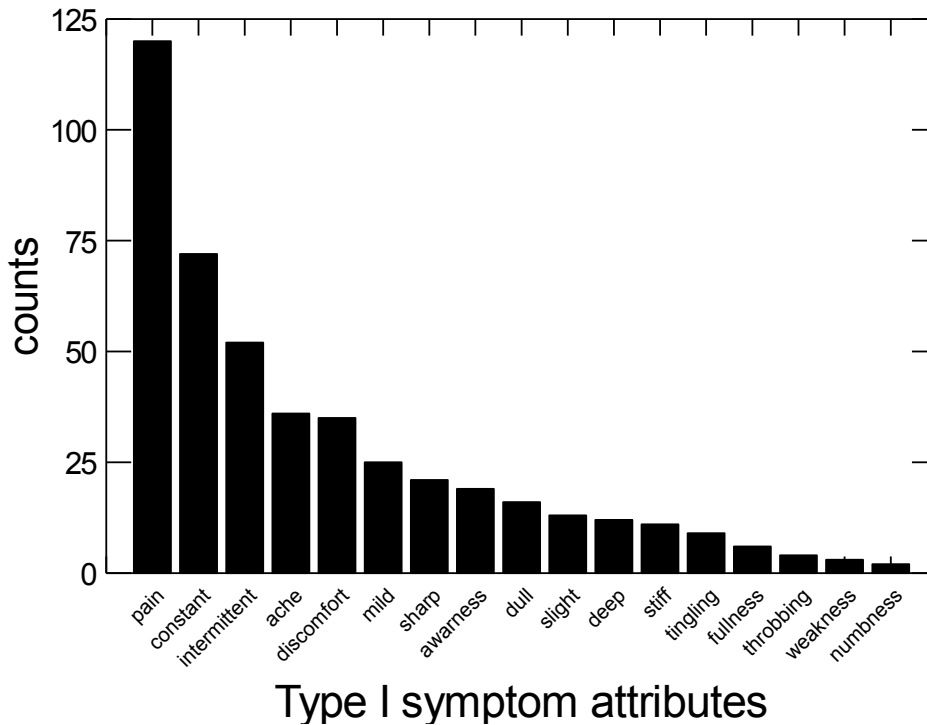
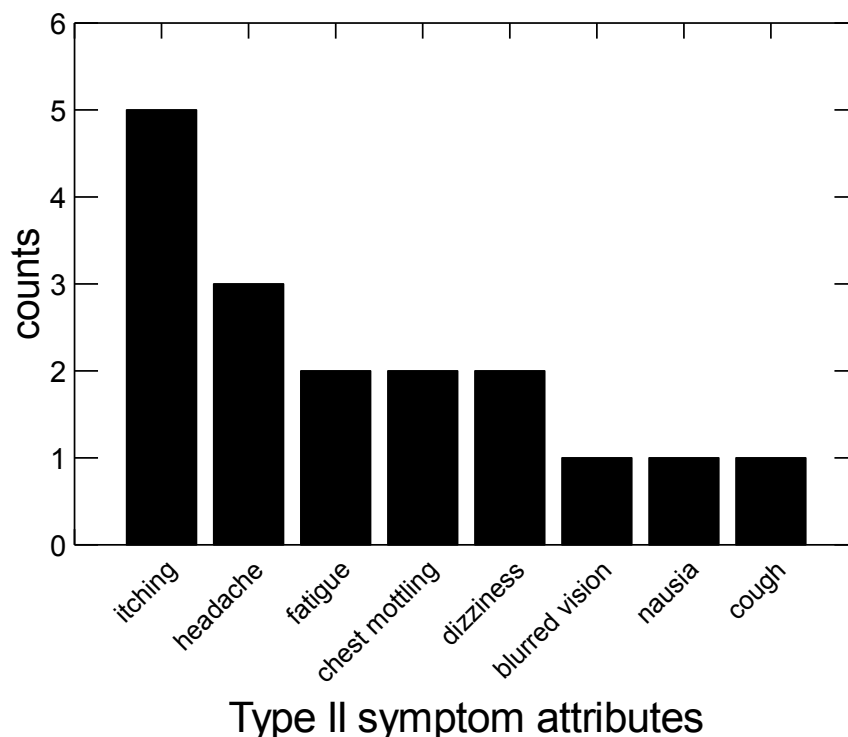


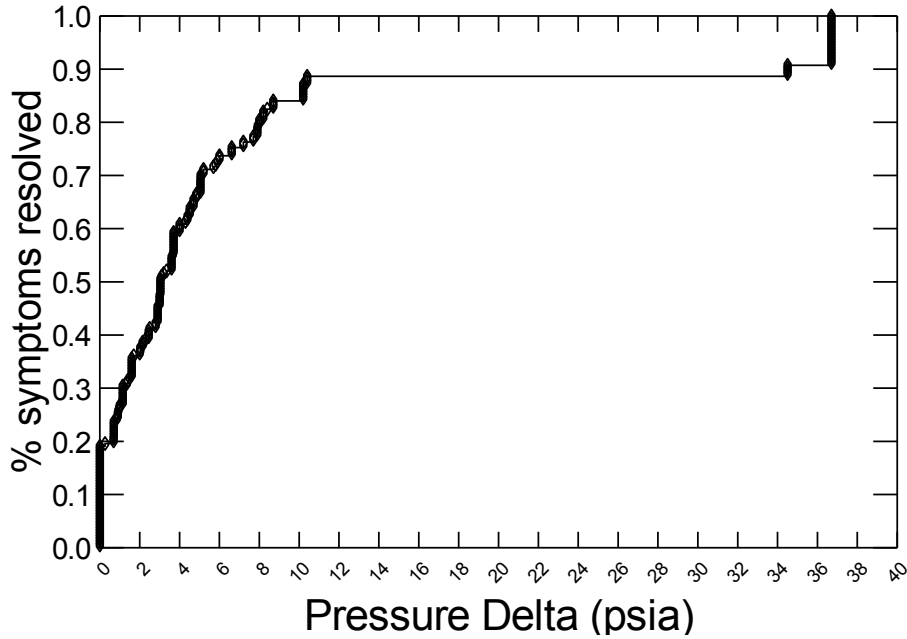
Figure 10. Number of Type I symptom attributes in 119 cases of DCS. Seven of the 9 records for “tingling” symptom came from one subject. The 2 symptoms of numbness were attributed to impaired circulation and not neurological in origin.

Figure 11 shows the number of Type II symptom attributes from 7 cases classified as Type II DCS. The low number of Type II symptoms limit any meaningful conclusions.



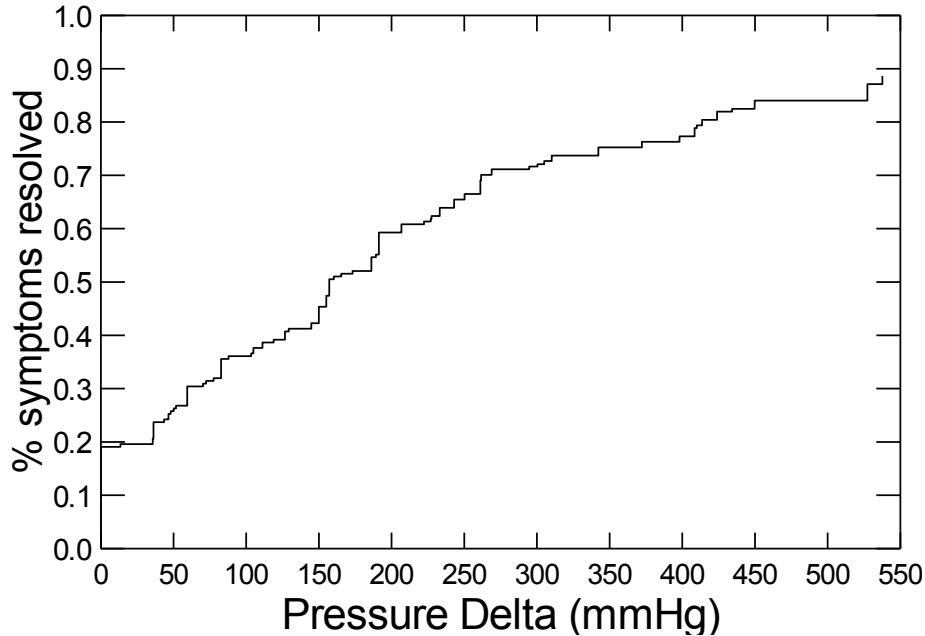
**Figure 11. One of 3 headaches here was classified as Type I DCS. Headache and a sensation of being hot during an otherwise unremarkable 4-hr test caused the symptom of “headache” to be classified as Type I DCS in a female. However, the subject later reported with Type I symptoms and underwent HBO treatment. Chest mottling (cutis marmorata) was initially classified as Type II DCS at JSC but now exists as its own category of DCS – not Type I or Type II. It is shown on this graph in its historical context.**

Once a symptom appears during a validation test it must be completely resolved before the subject is released by the Medical Officer. Figure 12 shows the cumulative percentage of symptoms that resolved at the given pressure difference. Thirty-seven symptoms (19%) resolved at the test altitude, before repressurization, 122 symptoms (63%) resolved during repressurization, 14 symptoms (7.2%) resolved at site pressure (14.5 to 14.7 psia), and 21 symptoms (10.8%) were persistent at site pressure and resolved during an HBO treatment (USN Treatment Table V or VI). Not represented on the figure are 11 symptoms that initially resolved prior to the subject being released from the test but reoccurred later and initiated HBO treatment. Given the lengthy denitrogenation provided to NASA subjects, 89% of 194 symptoms resolved over a pressure difference of 10.4 psia with 50% resolution over a pressure difference of just 3 psia.



**Figure 12. The cumulative percentage of 194 symptoms that resolved at the given pressure difference defined as the pressure at symptom resolution minus the altitude test pressure, in units of psia.**

Figure 13 shows NASA data about the cumulative percentage of 194 symptoms that resolved at a given pressure difference up to total recompression. A comparison of this NASA data to a much larger dataset of 1,699 resolved DCS symptoms from Muehlberger *et al.* (2004) reveals similarities despite about 9 times more data from Brooks AFB. For example, 19.0% of symptoms resolved at the test altitude in the NASA data compared to 4.4% in the USAF data and 81.9% of all symptoms in the NASA data resolved before reaching site pressure compared to 88.2% in the USAF data. Fifty percent of symptoms resolved in the NASA data after the application of 160 mmHg of pressure compared to 138 mmHg for the USAF data. Seventy-five percent of symptoms resolved in the NASA data after applying 340 mmHg of pressure compared to 250 mmHg for the USAF data.



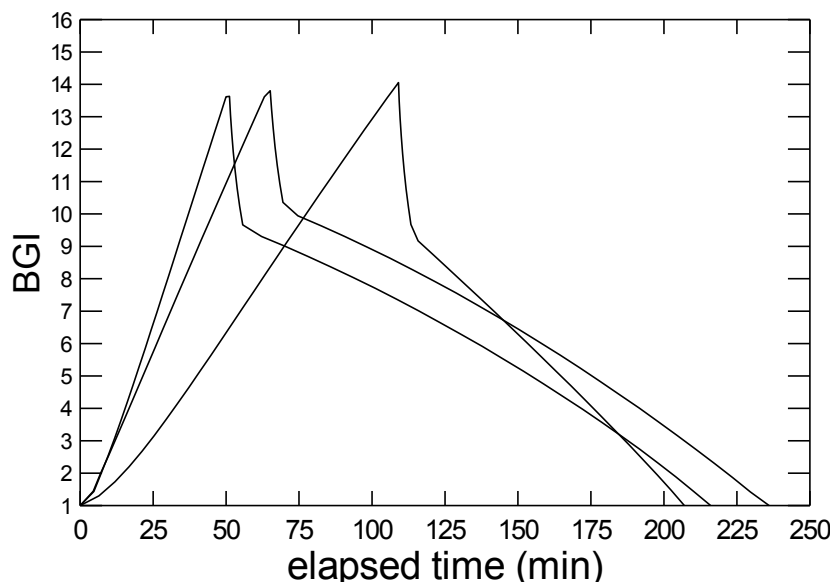
**Figure 13. The majority of data as in Figure 12 with expanded x-axis and pressure difference converted to mmHg unit.**

Figure 14 shows 3 examples to demonstrate the resolution of a Bubble Growth Index (BGI) of 14 units given a Boyle's Law decrease in bubble volume with applied treatment pressure and the bubble-to-tissue  $N_2$  gradient as computed with the BGI model (Gernhardt 1991). BGI is the ratio of final bubble radius to an initial bubble radius of 3 microns.

The first curve from left is after a 60 min PB in an astronaut exposed to 4.3 psia with return to 14.7 psia, the second curve is a saturation diver with return to 41.1 psia after exposure to 14.7 psia, and the third curve is after a 300 min PB in an astronaut exposed to 4.3 psia with return to 14.7 psia (5 min for all pressure transitions). The elapsed time from the start of decreased pressure (time 0) to bubble resolution is shorter in the astronaut cases, dependent on the PB time, compared to the saturation diver. The difference is due to a slight Boyle's Law advantage during the return to site pressure (14.7 psia for astronaut and 41.1 psia for saturation diver) combined with a greater bubble-to-tissue  $N_2$  gradient for the astronaut with the longer PB compared to the saturation diver.

A tentative conclusion based on only 3 examples and multiple assumptions in the BGI model is that the time is shorter to resolve a theoretical bubble for an astronaut treated with 100%  $O_2$  at 1 ATA compared to a saturation diver treated with 100%  $O_2$  at 2.8 ATA (his saturation pressure, and the treatment pressure for the USN TT V). One other complication for the diver is the high  $pO_2$  during treatment, a level that must be reduced during "air breaks" to prevent CNS or pulmonary  $O_2$  toxicity. This complexity was not included in the simulation and is not a complexity that the astronaut must face since 100%  $O_2$  at 1 ATA is well-tolerated for several hrs.

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**Figure 14. The resolution of a 14 unit BGI given a Boyle's Law decrease in bubble volume with applied treatment pressure and the bubble-to-tissue N<sub>2</sub> gradient. First curve from left is after a 60 min PB in an astronaut exposed to 4.3 psia with return to 14.7 psia, second curve is a saturation diver with return to 41.1 psia after exposure to 14.7 psia, and third curve is after a 300 min PB in an astronaut exposed to 4.3 psia with return to 14.7 psia (5 min for all pressure transitions).**

DCS treatment on ISS follows a flow diagram that treats symptoms and evolved gas by keeping the astronaut in the suit breathing 100% O<sub>2</sub> at 4.3 psid (19.0 psia) for prescribed intervals of time. A limited neurological examination is available that assesses the suited astronaut during the course of treatment. The return from 4.3 psia to even 14.7 psia on ISS causes a 71% Boyle's Law decrease in a unit volume of gas. This compares with a 64% decrease in a unit volume of gas in a diver that is treated at 2.8 ATA (41.1 psia). Remaining in the suit and pressurized to 19.0 psia causes a 77% decrease in a unit volume of gas. In the event symptoms do not resolve at 19.0 psia the Bends Treatment Adapter (BTA) is installed without depressurizing the suit. The suit is further pressurized to 8.0 psid (22.7 psia) resulting in an 81% decrease in a unit volume of gas, significantly better than a diver seeking treatment on a USN TT V. Although an effective treatment option, the use of the BTA results in EMU that is no longer certified for EVA. A return to site pressure (see Fig. 11) is expected to resolve most symptoms and the option to treat a persistent, recurrent or Type II symptom at 22.7 psia with 100% O<sub>2</sub> using the BTA is expected to be effective. The option to return an astronaut to Earth for additional treatment was possible with the shuttle from the ISS but is not an option with the Russian Soyuz and will not be an option on the Moon, Mars, or from deep space.

Providing DCS treatment options and any adjunctive therapy for Exploration Class missions should follow an evidence-based approach. The approach needs to ultimately match the most effective treatment to the anticipated risks since providing proper medical treatment at remote



locations is both costly and impacts the success of the mission (John-Baptiste *et al.* 2006, Rudge 1992, Krause & Pilmanis 2000, Dowell 1993, and Butler *et al.* 2002).

## **6 Risk in Context of Exploration Mission Operational Scenarios**

As of May 2016, there have been no reported cases of DCS during Shuttle and ISS missions due to adherence to PB protocols rigorously developed and validated specific to Shuttle and ISS operational environments and EVA scenarios. Although DCS risk has been greatly reduced through these PB protocols, it is at the expense of significant crew time and consumable usage. This need for significant crew time and consumables will not meet the needs of the Exploration program.

The architectures being developed by NASA for future exploration beyond low earth orbit differ from previous vehicles and EVA systems in terms of vehicle saturation pressures, breathing mixtures, EVA frequency, EVA durations, and pressure profiles, and will almost certainly differ in terms of the definition of acceptable DCS risk and in-situ DCS treatment capabilities. The use of suit ports, variable pressure EVA suits, intermittent recompressions, and possibly abbreviated purges with PB gas mixtures of less than 100% oxygen represent a paradigm shift in the approach to EVA with the potential of reducing EVA crew overhead and consumables usage by two orders of magnitude (Abercromby *et al.* 2015). However, the role and impact of these variables on the overall probability of DCS is theoretical, without empirical data to support the theory. In addition, DCS risk must always be balanced with the availability of treatment capability.

### **6.1 PB Protocols Meet Acceptable DCS Risk Level, but with Poor Work Efficiency Index (WEI) and High Consumables Use**

WEI is defined as EVA time divided by the amount of time spent preparing for the EVA, be it spent in a PB protocol or tasks related to an EVA suit preparation. NASA's historical  $\mu$ G EVA experience leads to an expectation of the threat of serious DCS being extremely small primarily due to rigorous adherence to validated PB protocols. Outside of the shuttle staged protocol, a unifying principle of all of these PB protocols is that there is a significant use of crewmember time and consumables before they exit the airlock. Current ISS WEI is less than 0.4. This WEI accounts for PB, suit donning/doffing and processing of the EVA suit and associated tools. While this is tolerable for ISS EVAs, primarily due to their low frequency and pre-existing EVA timelines, it will not be acceptable for future manned exploration missions, which will rely on a robust, efficient EVA program that assumes high-frequency flexible exploration objectives of the destination target(s). Architectural assumptions for future surface exploration missions include up to multiple EVAs per person per day, which is unachievable given current spacecraft atmospheres and prebreathe protocols.

## **6.2 Exploration Missions Need to Define WEI and EVA Goals**

There are several potential DRM destinations that lie ahead in NASA's manned exploration pathway. Each DRM has its own unique combination of DCS risk factors and how NASA plans on countering those problems must be considered in advance of final design plans for manned mission elements. Prescribing an expected WEI target for any given DRM would drive overall design and engineering towards the most efficient use of crewmember time.

An efficient exploration program needs an efficient EVA component. Infrequent, highly specific EVAs such as those performed for ISS assembly were effectively managed using existing PB protocols. Exploration missions will not have these same highly specified EVA timelines, but plan to rely on more real-time science objectives and prioritization to determine EVA needs. While there are different ways to manage exploration EVA, the most flexible approach is to determine a minimal denitrogenation strategy that allows for on-demand EVA capabilities. This will most likely be met with some sort of staged denitrogenation protocol. Currently, a long PB time is needed before EVA from the ISS. The denitrogenation may be effective to reduce the P(DCS), but even effective existing 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 (Foster *et al.* 2003, Moon 2000, Pilmanis *et al.* 1996).

A future habitat atmosphere should have a low  $pN_2$  to shorten or eliminate the PB time. One practical approach to reduce the  $pN_2$  is to increase the  $pO_2$  while also reducing the ambient pressure (Allen *et al.* 1969, Cooke & Robertson 1974, Horrigan & Waligora 1980). A balance is achieved between the increased risk of fire at high  $O_2$  concentration and the decreased risk of DCS as  $pN_2$  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  $P_1O_2$  is less than 150 mmHg, but not so low as to cause significant hypoxia (Conkin & Wessel 2008). Not considered here are 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 (Brown *et al.* 1991, Campbell 2006), problems with voice communication (Roth 1967), and reduced available response time in the event of a cabin atmosphere leak.

## **6.3 Mitigating DCS through an Exploration Atmosphere may Introduce New Concerns**

The Engineering Directorate, Space and Life Sciences Directorate, Extravehicular Activity Office, and Astronaut Office all approved the proposed Exploration Atmosphere (8.0 psia / 32%  $O_2$ ) which was a result of the 2006 Exploration Atmospheres Working Group (EAWG). This sought after compromise provided a balance between mild hypoxia ( $P_1O_2 = 117$  mmHg), flammability concerns in the pressurized living space and the availability of quick, low overhead EVA capability with the trade of very little DCS risk (Campbell, 2006). In 2012, the results of the EAWG were re-evaluated by the Exploration Atmosphere Action Team. The Human Health and Performance subteam had the specific focus of evaluating the hypoxic symptoms potentially associated with the 8/32 atmosphere. This effort resulted in a recommendation to raise the

pressure to 8.2 psia and O<sub>2</sub>% to 34%, resulting in a P<sub>1</sub>O<sub>2</sub> = 128 mmHg and no net change to the pN<sub>2</sub> (Norcross et al. 2013). When coupling the 8.2/34 Exploration Atmosphere with a variable pressure EVA suit and a highly efficient suit donning/doffing technology such as suitports, crew time and consumables use is efficiently maximized (Abercromby *et al.* 2015). However, there are undesired outcomes as well. In order to meet the demands of decreased pressure and acceptable flammability risk, crewmembers will live in mild hypoxia. This may result in unrealized (or perhaps, poorly understood) health consequences or crewmembers may acclimate quickly with no hypoxic symptoms. Astronauts experienced a very similar hypoxic stress during the shuttle staged protocol at 10.2 psia / 26.5% O<sub>2</sub> environment (P<sub>1</sub>O<sub>2</sub> = 127 mmHg). This level of hypoxia was not originally considered severe enough to warrant any specific research efforts. However, data mining efforts through the Lifetime Surveillance of Astronaut Health (LSAH) and Life Science Data Archive (LSDA) repositories are currently underway to determine any evidence of hypoxia related symptoms occurrence during these flights.

The Exploration Atmosphere Evidence Book documents more details about positive and negative synergy between hypoxia and  $\mu$ G adaptation (Norcross *et al.* 2015). But here we document the few historical reports where head-down tilt or simply inactive bedrest were used as analogues to  $\mu$ G combined with hypoxia, with P<sub>1</sub>O<sub>2</sub> much less than the proposed 128 mmHg (Stevens *et al.* 1966, Lynch *et al.* 1967, Waligora *et al.* 1982, Fulco *et al.* 1985, Loeppky *et al.* 1993, 1993a). There are several examples where the physiological changes initiated by hypobaric hypoxia and adaptation to  $\mu$ G are in opposite directions. Therefore, the net effect is a blunted response when both conditions occur simultaneously (Conkin 2008). Some even propose that the compensations for hypobaric hypoxia provide a beneficial therapy for cardiovascular deconditioning associated with extended bedrest (Lamb 1965, Lynch *et al.* 1967, Shvartz 1990).

We also document recent research from European investigators who anticipate that mild hypoxia may be part of the strategy for future exploration atmospheres. This is a strategy to reduce pN<sub>2</sub> in a hypobaric environment and therefore the risk of DCS during EVA, conserve O<sub>2</sub> otherwise needed for prebreathe, and to minimize the risk of fire. The 36<sup>th</sup> Annual International Gravitational Physiology meeting (<http://www.isgp2015.org/programme/>) in Ljubljana, Slovenia in 2015 hosted a poster session titled, “Hypoxic bedrest: simulation of lunar and planetary habitats.” Seven posters on hypoxia-bedrest interactions were presented, possibly leading to papers in 2016. Changes in body composition during extended bedrest were not exacerbated by hypoxia (Debevec *et al.* 2014, 2014a). It follows from a review of limited data that the addition of hypoxia does not have a strong positive or negative effect on adaptive changes to simulated  $\mu$ G and *vice versa*, even at P<sub>1</sub>O<sub>2</sub> less than that proposed for the 8.2 psia 34% O<sub>2</sub> (P<sub>1</sub>O<sub>2</sub> = 128 mmHg) exploration atmosphere. On balance, there is no definitive evidence for an *exaggerated* (negative synergistic) response to the combination of mild hypobaric hypoxia and adaptation to  $\mu$ G (Norcross *et al.* 2015, Wessel *et al.* 2015). On the contrary, the limited evidence suggests that one stressor tends to counteract the other (Conkin 2008). The benefit of mild hypoxia to facilitate frequent and efficient EVAs must be balanced with any undesirable changes to homeostasis and to the extent to which those changes can be mitigated.

## **6.4 No Exploration Atmosphere Means Longer Denitrogenation Protocols and Higher Consumables Usage**

Current and future spacesuit functionality requires decompression to perform EVA. Without the use of a staged denitrogenation protocol, such as proposed with the 8.2/34 Exploration Atmosphere, or a zero-PB EVA suit operating at higher pressures, denitrogenation protocols will remain lengthy. Much research could be performed to reduce the length of existing ISS PB protocols. Understanding how a break in PB affects P(DCS) would be a critical step. Also, understanding the differences in VGE, N<sub>2</sub> washout and micronuclei generation in the space flight environment would be of great benefit. In the end, an operational mitigation strategy that relies on long O<sub>2</sub> PB as the primary strategy will result in longer more complicated EVA preparation timelines, higher consumables use and reduce the flexibility and capabilities of Exploration EVA.

An example of the consumables savings available through use of the 8.2/34 Exploration Atmosphere is by reducing the suit purge time by 6 min per EVA, achieving 80% O<sub>2</sub> in the spacesuit rather than 95%. This modestly increases P(DCS) risk but the calculated savings of 0.48 lb of gas and 6 minutes per person per EVA corresponds to more than 31 hours of crew time and 1800 lb of gas and tankage under the Constellation lunar architecture (Abercromby *et al.* 2015).

Of available strategies to significantly reduce denitrogenation time while maintaining acceptable DCS risk, the Exploration Atmosphere strategy is more promising than either a high pressure EVA suit or an enhanced version of current ISS PB protocols.

## **6.5 DCS Treatment is Undefined**

NASA operates under the maxim that prevention of DCS is better than treatment of DCS. Nowhere is that statement truer than when astronauts are far beyond Low Earth Orbit, and effectively outside the reach of real-time medical guidance. NASA should make every attempt to first use engineering controls and then operational procedures to mitigate DCS to acceptable risk levels and then properly prepare to treat a symptomatic crewmember. There may be no hyperbaric chamber capability available during future exploration missions, but if properly designed, a variable pressure suit port compatible EVA suit could provide almost instantaneous repressurization to the intermediate habitat pressure (likely 8.2 psia) and, if detached from the suit port and brought inside the cabin, could provide at least an additional 8.2 psia above the ambient cabin pressure. This simple application of Boyle's Law goes a considerable distance in resolving most Type-I DCS pain (see Section 5 DCS Treatment Experience).

## **7 Gaps**

We have described much of the evidence related to spaceflight DCS, and there still remain gaps in knowledge. The gaps are described in the following sub-sections and form the focus on the future NASA DCS research efforts.

## **7.1 DCS1 – We have not defined the acceptable DCS risk with respect to the work efficiency index (WEI) for exploration scenarios.**

Acceptable DCS risk for ISS assembly was defined as part of the PB reduction program. By validating operational PB protocols against this acceptable risk level, NASA has successfully prevented both serious Type II DCS and Type I pain only DCS. This acceptable risk level was reviewed by the NASA Headquarters Chief Health and Medical Office and included as a new human spaceflight standard in the EVA section of NASA-STD-3001 Volume 1. This standard dictates the minimum standard for which all future PB protocols will need to test against. The focus of this standard was to protect against long and short term human health consequences, but it does not define any guidelines for WEI, crew time or consumables.

The target for gap closure included this the NASA-STD-3001 Volume 1 update for EVA purposes, but also includes a later update to NASA-STD-3001 Volume for a DCS risk standard related to vehicle decompressions to the Exploration Atmosphere, which exposes the whole crew to a DCS risk. An additional metric to consider would be the acceptable risk for contingency EVA scenarios. Currently, all contingency scenarios are handled as isolated events, but a pre-determined level of acceptable risk for contingency EVA and a supporting higher risk, but lower overhead PB protocol would be worth considering.

## **7.2 DCS2 – We do not know the contribution of specific DCS risk factors to the development of DCS in the Space Flight Exploration Environment.**

As previously discussed, it is well accepted that gas bubbles through some mechanism are the initial cause of the symptoms of DCS. This gas bubble formation and growth can potentially occur during decompressions from higher to lower ambient pressure, but the mechanisms that cause bubble formation, growth and elimination are not well understood. It is known that physiological and environmental factors contribute to DCS, but there is a lack of information on their importance or interrelationships in the space flight environment.

The target for gap closure is to obtain an effect size as a function of individual variance for each risk factor of interest. Depending on the statistical significance of a given risk factor, it may then be included in a comprehensive DCS prediction model.

## **7.3 DCS3 – We do not know the mission related factors that contribute to DCS risk.**

The characteristics of the ISS EVA environment are well understood, but this is not the case with new DRMs. For instance, it is known that activity level during depressurization has a significant effect on the development of DCS. At any given depressurization, an increase in activity level increases the DCS risk. In addition, certain movements tend to be more provocative than others, possibly due to the forces generated by movement in different joints. NASA is going to locations where there is either no or little human EVA experience. Many factors contribute to DCS risk

and all of these factors need to be understood in order to provide updates to models and/or to the development of EVA simulators for PB validation trials.

The target for gap closure is to develop an EVA simulator for use in PB validation trials; to provide inputs related to WEI, EVA overhead, crew time and consumables usage in relation to achieving acceptable DCS risk (Gap 1); and to obtain an effect size as a function of individual variance for each risk factor of interest in order to consider for inclusion in a comprehensive DCS prediction model.

#### **7.4 DCS4 – We do not know to what extent physiological and environmental factors can be incorporated and validated in a model of DCS for micro and reduced gravity.**

Existing DCS prediction models have differing levels of credibility for  $\mu$ G EVA from an Earth normal atmosphere habitat, but none of these models are validated for the Exploration environments including planetary gravity, 8.2/34 Exploration Atmosphere, and high-frequency EVA. Research efforts are underway to define a DCS treatment model. There is also a need for a comprehensive DCS prediction model that is both user-friendly and applicable across all DRMs. Finally, a tissue saturation model is proposed to understand tissue saturation rates with- and without exercise conditions.

The target for gap closure are validated DCS risk and DCS treatment models for the expected Exploration environments, which meets requirements of NASA-STD-7009.

#### **7.5 DCS5 – We do not know what validated procedures will adequately prevent DCS.**

Validated procedures to prevent DCS exist for the ISS, but not for Exploration Mission DRMs. Current DCS prediction models do not extrapolate to the expected Exploration environment and can only be used to develop initial estimates for Exploration protocols which must be validated through ground testing prior to operational implementation.

The targets for gap closure are PB protocols that meet the DCS1 acceptable risk standard for future exploration missions.

#### **7.6 DCS6 – We do not know what new developments related to DCS will come from other investigators.**

Through active involvement in DCS research for the past 30 years, the current status of DCS risk factors, treatment modalities, detection methods and prediction models are well known to NASA, but NASA is not the only institution performing DCS research. There remains a solid academic, military and aerospace presence interested in DCS and their developments need to be closely monitored.

The target for this gap closure is automatically met assuming the HRP EVA Discipline team regularly reviews the scientific literature and attends relevant scientific meetings. Closure is also met through regular research plan reviews by external experts as per HRP policy.

### **7.7 DCS7 – We have not validated procedures to adequately treat DCS in the spaceflight environment should it occur.**

DCS treatment protocols for altitude DCS often involve hyperbaric oxygen treatment. These treatment protocols are based on aviation scenarios and assume a crewmember's return to ground. In space, this may not be possible and we need to understand the capabilities of treating DCS with the use of expected in-situ resources.

Additionally, we need to consider if there are any long term outcomes of spaceflight DCS that need to be followed over the course of a crew member's life.

The target for gap closure would be inputs to DCS treatment procedures for each DRM and recommendations to the LSAH project for medical tests needed to evaluate long term health consequences of spaceflight DCS.

## **8 Conclusion**

DCS is an occupational health and mission hazard that requires mitigation as an astronaut moves from a higher pressure habitat into the lower pressure EVA suit. To date, DCS has been effectively mitigated through rigorous adherence to PB protocols validated specific to the  $\mu\text{G}$  EVA environment. While effective, these protocols are complex and require significant pre-flight training, inflight crew time and consumables usage. Furthermore, utilization of the Exploration Atmosphere (8.2 psi / 34%  $\text{O}_2$ ), suit ports, variable pressure suits, and the inability to rapidly deorbit for medical treatment mean that existing DCS risk mitigation protocols and data sets are not applicable to future exploration missions.

The acceptable risk for DCS has been defined in the NASA Human Spaceflight Standards, therefore, the next step will be to develop and validate procedures, protocols, and countermeasures to meet this standard effectively and efficiently for the range of nominal and off-nominal atmospheres and decompression profiles that crewmembers may experience during future exploration missions.

To improve efficiency from a sea level atmosphere, data is needed on the potential differences in bubble formation and  $\text{N}_2$  elimination while in  $\mu\text{G}$ . To improve safety and efficiency from any atmosphere, data is needed to describe the consequences of a break in prebreathe. Finally, the opportunity exists to mitigate DCS primarily through engineering controls by the use of the 8.2 psia / 34%  $\text{O}_2$  Exploration Atmosphere, suit ports, and variable pressure EVA suits. While promising, these technologies are poorly understood from a physiological perspective and will demand rigorous development and testing of DCS mitigation strategies and procedures prior to operational implementation.

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Many more than those listed above have contributed to the DCS Evidence Book. It is impossible to acknowledge by name all those involved in the testing, training, and operational implementation of denitrogenation protocols used in more than 40 years of spacewalks from the Gemini, Apollo, Skylab, Shuttle, Russian *Mir* space station, and International Space Station programs.

## **11 List of acronyms**

1-G	Earth-normal gravity
AFB	Air Force Base
AGE	arterial gas emboli
Ar	argon
ATA	atmosphere pressure absolute
ATM	atmosphere pressure
BGI	bubble growth index
BMI	body mass index
BTA	bends treatment adapter
CEVIS	cycle ergometer with vibration isolation and stabilization
CM	cutis marmorata
CNS	central nervous system
CO <sub>2</sub>	carbon dioxide
DCS	decompression sickness
DCIEM	Defense and Civil Institute of Environmental Medicine
ΔP	pressure difference
DT	Doppler technician
EMU	Extravehicular Mobility Unit
ETA	environmental test article
EVA	extravehicular activity
FFW	feet fresh water
FN <sub>2</sub>	fraction of nitrogen in a bubble
FSW	feet sea water
ft	foot
GLO	ground level oxygen
HBO	hyperbaric oxygen
hr	hour
HRP	Human Research Program
ID	identification
ISLE	in-suit light exercise
ISS	International Space Station
JSC	Johnson Space Center
kg	kilogram
k	number of gas species in tissue
kPa	kilopascal
lbf	pound force
μG	microgravity
m	meter
min	minute
ml	milliliter
mmHg	millimeters of mercury (pressure)
MO	Medical Officer

*Risk of Decompression Sickness (DCS)*

MP	microparticles
MRI	magnetic resonance imaging
n	sample size
N	Newtons of force
NASA	National Aeronautics and Space Administration
NBL	Neutral Buoyancy Laboratory
NEEMO	NASA Extreme Environment Mission Operations
N <sub>2</sub>	nitrogen
O <sub>2</sub>	oxygen
P1	initial pressure
P1N <sub>2</sub>	computed tissue N <sub>2</sub> partial pressure
P2	final pressure
PB	prebreathe
P(DCS)	probability of decompression sickness
P(Grade IV VGE)	probability of Grade IV VGE
PI	Principal Investigator
P(Serious DCS)	probability of serious decompression sickness
PFO	patent foramen ovale
P <sub>i</sub> N <sub>2</sub>	inspired (wet) partial pressure of nitrogen
P <sub>i</sub> O <sub>2</sub>	inspired (wet) partial pressure of oxygen
pN <sub>2</sub>	partial pressure of nitrogen
pO <sub>2</sub>	partial pressure of oxygen
PRP	Prebreathe Reduction Protocol
psia	pounds per square inch absolute
PTC	Physiological Training Chamber
r <sub>c</sub>	critical radius
R-value	ratio-value used by NASA, equivalent to P1N <sub>2</sub> / P2
SCUBA	self-contained underwater breathing apparatus
SD	standard deviation
STPD	standard temperature (0 Celsius), pressure (1 ATM), dry gas
STS	Space Transportation System
TR	tissue ratio
TT V	Treatment Table V
TT VI	Treatment Table VI
U.S.	United States
USAF	United States Air Force
USN TT V	United States Navy Treatment Table V
VGE	venous gas emboli
VO <sub>2</sub> peak	measured peak oxygen consumption as ml*kg <sup>-1</sup> *min <sup>-1</sup>
WMH	white matter hyperintensities
WW II	World War II



## **Appendix A: Computer-based DCS Modeling: Description of Models**

Data collected from 1982 to present are archived in the JSC Hypobaric Decompression Sickness Database. Results from specific PB protocols were used to accept or reject the protocol for specific applications. Since each protocol is unique, it is also possible to statistically describe large subsets of data to create predictive equations (models), which we call Probabilistic Modeling. We have created two classes of predictive models: statistical and biophysical. The statistical models compute the probability of DCS given information from our best research data, and best published data in cases where our research data is insufficient to address an issue. We have also extended the methodology to create a probability model for acute mountain sickness, a transient possibility on future exploration missions. The biophysical (bubble) models give us information about bubble growth in tissue, which is then linked to the probability of DCS through logistic regression, or even through a statistical survival model.

Variables that describe a test are combined to create a decompression dose. For each dose there is a DCS and VGE response, or outcome. The statistical process optimizes the expression for dose to compute the best probability for the response. The dose includes information about the PB procedure (exercise and rest intervals), the suit pressure, the time spent at altitude, if exercise is done at altitude, sometimes information about the person in the test (VO<sub>2</sub> peak, gender, age), and if the test was done under a microgravity simulation (adynamia).

There are multiple probability models available to us through the years that describe the risk of DCS, forced descent DCS, serious DCS, VGE, Grade IV VGE. Most, but not all, of these models are documented as contractor reports or science journal publications, and most are contained in the ATOM program, but additional BASIC programs have been written to compute 95% confidence intervals for best estimate of risk that are not part of the ATOM program. As new data become available, statistical and biophysical predictive models are updated. The following is a summary list of statistical probability models available to us to evaluate new potential PB protocols before a new protocol is proposed for testing.

### **Hill Equation Model for total DCS and VGE, n = 927**

### **Hill Equation Model for symptoms that would stop an EVA, n = 698**

Reference: Conkin J, BF Edwards, JM Waligora, J Stanford, Jr., JH Gilbert, III, DJ Horrigan, Jr. Updating empirical models that predict the incidence of aviator decompression sickness and venous gas emboli for shuttle and space station extravehicular operations. NASA Technical Memorandum 100456 Update, Johnson Space Center, Houston, Tx. October 1990. Regression contained in the ATOM program.

### **Survival DCS Model, n = 1075**

## *Risk of Decompression Sickness (DCS)*

Reference: Conkin J, KV Kumar, MR Powell, PP Foster, JM Waligora. A probability model of hypobaric decompression sickness based on 66 chamber tests. *Aviat. Space Environ. Med.* 1996; 67:176-83.

Regression contained in the ATOM program.

Reference: Thompson LA, Chhikara RS, Conkin J. Cox proportional hazards models for modeling the time to onset of decompression sickness in hypobaric environments. NASA Technical Publication 2003-210791, Houston: Johnson Space Center, March 2003.

Reference: Thompson LA, Chhikara RS, Conkin J. Evaluation of Cox proportional hazards models for time to onset of decompression sickness in hypobaric environments. ISSO Y2002 Annual Report, Houston: University of Houston and University of Houston at Clear Lake, p. 13-20, Spring 2003.

### **Survival DCS Model, n = 968**

Reference: Conkin J, Abercromby AFJ, Dervay JP, Feiveson AH, Gernhardt ML, Norcross JR, Ploutz-Snyder R, Wessel JH, III. Hypobaric decompression sickness treatment model. *Aerosp Med Hum Perform* 2015; 86:508-17.

Reference: Conkin J, Abercromby AFJ, Dervay JP, Feiveson AH, Gernhardt ML, Norcross J, Ploutz-Snyder R, Wessel JH, III. Probabilistic assessment of treatment success for hypobaric decompression sickness. Houston, TX: NASA Johnson Space Center; November 2014. NASA Technical Publication NASA/TP-2014-218561.

### **Survival DCS Model (break in prebreathe), n = 207**

Reference: Conkin J. Decompression sickness after air break in prebreathe described with a survival model. *Aviat Space Environ Med* 2011; 82:589-98.

### **Survival VGE Model, n = 842**

Reference: Conkin J, Abercromby AFJ, Dervay JP, Feiveson AH, Gernhardt ML, Norcross J, Ploutz-Snyder R, Wessel JH, III. Probabilistic assessment of treatment success for hypobaric decompression sickness. Houston, TX: NASA Johnson Space Center; November 2014. NASA Technical Publication NASA/TP-2014-218561.

### **Forced Descent DCS Model, n = 4766**

Reference: Van Liew HD, Burkard ME, Conkin J. Testing of hypotheses about altitude decompression sickness by statistical analyses. *Undersea Hyperbaric Med.* 1996; 23:225-33. Regression contained in the ATOM program.

### **Adynamia DCS and VGE Models, n = 1401**

## *Risk of Decompression Sickness (DCS)*

Reference: Conkin J, Powell MR. Lower body adynamia as a factor to reduce the risk of hypobaric decompression sickness. *Aviat. Space Environ. Med.* 2001; 72:202-14.  
Regression contained in the ATOM program.

### **Serious DCS Model, n = 79,366**

Reference: Conkin J. Evidence-based approach to the analysis of serious decompression sickness with application to EVA astronauts. NASA Technical Publication 2001-210196, Houston: Johnson Space Center, January 2001.  
Regression contained in the ATOM program.

Reference: Thompson LA, Chhikara RS, Conkin J, Powell MR. Determination of risk of serious decompression sickness among astronauts involved in space extravehicular activity. ISSO Y2001 Annual Report, Houston: University of Houston and University of Houston at Clear Lake, p. 82-84, Spring 2002.

Reference: Conkin J, Klein JS, Acock KE. Description of 103 cases of hypobaric decompression sickness from NASA-sponsored research (1982 to 1999). NASA Technical Publication 2003-212052 Houston: Johnson Space Center, July, 2003.

### **Grade IV VGE Model, n = 549 (NASA only data)**

Reference: Conkin J. unpublished regression given the age, tissue ratio, duration of the exposure, and if the subject was adynamic or not during the exposure.  
Regression contained in the ATOM program.

Reference: Thompson LA, Conkin J, Chhikara RS, Powell MR. Modeling Grade IV venous gas emboli using a limited failure population model with random effects. NASA Technical Publication 2002-210781, Houston: Johnson Space Center, June 2002.

Reference: Conkin J, Powell MR, Gernhardt ML. Age affects severity of venous gas emboli on decompression from 14.7 to 4.3 psia. *Aviat. Space Environ. Med.* 2003;74:1142-1150.  
Note: the model does not include an expression for tissue ratio, so any comparison of observed Grade IV to these estimates must be from tests “like” the tests used in this model. This means resting and exercise prebreathes > 180 min.

Reference: Thompson LA, Chhikara RS, Conkin J, Powell MR. A limited failure population model for onset of Grade IV venous gas emboli. ISSO Y2001 Annual Report, Houston: University of Houston and University of Houston at Clear Lake, p. 22-29, Spring 2002.

### **Cuff 1, 2, 4 (NASA), 4(literature) DCS Models, n=194, 914, 914, 6859**

Reference: Conkin J. unpublished regressions given only tissue ratio.  
Regression contained in the ATOM program.

### **Exercise Adynamia DCS Models (NASA, n = 154) and (Research, n = 222) from PRP Data**

## *Risk of Decompression Sickness (DCS)*

Reference: Conkin J, Gernhardt ML, Powell MR, Pollock N. A probability model of decompression sickness at 4.3 psia after exercise prebreathe. NASA Technical Publication NASA/TP-2004-213158 Houston: Johnson Space Center, December 2004.

### **Exercise Adynamia DCS Models (NASA, n = 204) from PRP Data (at conclusion of V-5 test)**

Reference: Conkin J. unpublished regressions given only exercise tissue ratio.

### **USAF Altitude Decompression Sickness Risk Assessment Computer (ADRAC)**

Note: Computer program on PC, but has limited application to NASA EVA program.

Reference: Pilmanis AA, Petropoulos LJ, Kannan N, Webb JT. Decompression sickness risk model: development and validation by 150 prospective hypobaric exposures. Aviat Space Environ Med 2004; 75:749-59.

### **Bubble Growth Index Model - biophysical bubble model optimized to predict hypobaric DCS**

Reference: Abercromby AFJ, Conkin J, Gernhardt ML. Modeling a 15-min extravehicular activity prebreathe protocol using NASA's exploration atmosphere (56.5 kPa / 34% O<sub>2</sub>). Acta Astronautica 2015; 109:76-87.

Note 1: model is currently optimized to subset of NASA DCS data, with plans to include relevant USAF data in the Air Force Research Laboratory Altitude Decompression Sickness Research Database archived at Wright-Patterson AFB. Model has the provision to account for exercise during prebreathe, but not a micronuclei size distribution.

Reference: Gernhardt ML. Development and evaluation of a decompression stress index based on tissue bubble dynamics. [Dissertation]. Philadelphia, PA: University of Pennsylvania, 1991.

Note 2: Dr. Srinivasan made significant advances in the biophysical description of bubble growth in tissue, but has since retired and did not leave any useful computer code or predictive equation based on optimizing his bubble model to empirical data. For completeness, two of his published works are documented:

Reference: Srinivasan RS, Gerth WA, Powell MR. Mathematical model of diffusion-limited evolution of multiple gas bubbles in tissue. Ann Biomed Eng 2003; 31:471-81.

Reference: Srinivasan RS, Gerth WA, Powell MR. A mathematical model of diffusion-limited gas bubble dynamics in unstirred tissue with finite volume. Ann Biomed Eng 2002; 30:232-46.

### **P(Symptom Resolution), n = 154 NASA and 1709 combined NASA + USAF**

## *Risk of Decompression Sickness (DCS)*

Reference: Conkin J, Abercromby AFJ, Dervay JP, Feiveson AH, Gernhardt ML, Norcross JR, Ploutz-Snyder R, Wessel JH, III. Hypobaric decompression sickness treatment model. *Aerosp Med Hum Perform* 2015; 86:508-17.

Reference: Conkin J, Abercromby AFJ, Dervay JP, Feiveson AH, Gernhardt ML, Norcross J, Ploutz-Snyder R, Wessel JH, III. Probabilistic assessment of treatment success for hypobaric decompression sickness. Houston, TX: NASA Johnson Space Center; November 2014. NASA Technical Publication NASA/TP-2014-218561.

### **Probability Model to Predict Acute Mountain Sickness**

Note: Living at high altitude with enriched O<sub>2</sub> atmosphere is still mildly hypoxic if you are to avoid increase in flammability in future spacecraft atmospheres. It is unclear what the true hypoxic dose is under these NASA-unique conditions. A non-validated statistical regression model based on limited data is available to assess the probability of acute mountain sickness.

Reference: Conkin J, Wessel JH III. Critique of the equivalent air altitude model. *Aviat Space Environ Med* 2008; 79:975-82.

Reference: Conkin J, Wessel JH III. A model to predict acute mountain sickness in future spacecraft. NASA Technical Publication NASA/TP-2009-214791, Houston: Johnson Space Center, July 2009.

### **Unit Pulmonary Toxicity Dose (UPTD) Model**

Note: The use of 100% O<sub>2</sub> in aerospace applications causes concerns about O<sub>2</sub> toxicity. A mathematical expression of UPTD is available to us to address concerns about limits to hyperbaric O<sub>2</sub> exposure.

Reference: Lambertsen CJ, Clark JM, Gelfand R, Hopkins E. Improved pulmonary O<sub>2</sub> toxic dose/effect prediction. Annual Meeting of the Undersea and Hyperbaric Medical Society, abstract #33, p. 19, June 26-29, 1999.

Regression contained in the ATOM program.