Individual Susceptibility to Hypobaric Environments: An Update

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ABSTRACT

Astronauts are at risk for developing decompression sickness (DCS) while exposed to the hypobaric environment of the extravehicular suit in space, in terrestrial hypobaric chambers, and during ascent from neutral buoyancy training dives. There is increasing recognition that DCS risk is different between diving and altitude exposures, with many individual parameters and environmental factors implicated as risk factors for development of DCS in divers but are not recognized as risk factors in altitude exposures. Much of the literature to date has focused on patent foramen ovale (PFO), which has long been considered a major risk factor for DCS in diving exposures, but its link to serious DCS in altitude exposures remains unclear. Knowledge of those risk factors specific to hypobaric DCS may help identify susceptible individuals and aid in astronaut selection, crew assignment, and mission planning. This paper reviews the current literature pertaining to these risk factors, including PFO, anthropometric parameters, gender, menstrual cycle, lifetime diving experience, physical fitness, biochemical levels, complement activation, cigarette smoking, fluid balance, and ambient temperature. Further research to evaluate pertinent risk factors for DCS in altitude exposures is recommended.

INTRODUCTION

Absolute or relative reductions in ambient pressure, as experienced during extravehicular activity, physiological training in hypobaric chambers, or ascent from diving place unique stressors on the human body. Participants in these environments are at risk for the development of decompression sickness (DCS), whose symptoms range from mild musculoskeletal pain to serious neurological deficits to death. Given the potential negative impact on crew health and mission success, it would be invaluable to identify risk factors for DCS and employ preventive strategies to mitigate the risk.

DCS occurs as a result of transitioning from one environment to a more hypobaric environment. When the ambient pressure decreases, nitrogen dissolved in the bloodstream comes out of solution and forms bubbles, which may remain locally or may be transported into the venous system. Most bubbles are trapped in the pulmonary capillary bed before being quickly resorbed, but if the pulmonary filter gets overwhelmed or bypassed due to an anatomic defect allowing for right-to-left shunt, these bubbles may become arterial gas emboli and result in local ischemia anywhere in the body.

:KLOH□7\SH□,□'&6□□³SDLQ□RQO\ or mild lymphatic involvement) generally requires no treatment or brief treatment with 100% oxygen, Type II DCS can manifest with pulmonary, cardiovascular, or neurologic symptoms that are more difficult to treat and may result in significant morbidity or mortality (Francis 1990). The Exploration Medical Capability Program has been tasked with reviewing what is known about individual susceptibility to hypobaric environments² specifically, DCS. This white paper will summarize the work done by the Patent Foramen Ovale Committee and Medical Operations EVA Integrated Product Team in 1999, review the literature on PFO since 1999, and discuss other risk factors for DCS that have been proposed.

PATENT FORAMEN OVALE & DECOMPRESSION SICKNESS

Patent foramen ovale (PFO), the primary means of arterial gas embolism through the heart that has been implicated in an LQGLYLGXDO¶V□VXVFHSWLELOLW\□WR□'&6□LV□D common remnant of fetal circulation when the atrial septum primum and septum secundum fail to fuse during the first months of life, enabling abnormal blood flow between the left and right atria. Some PFOs open only when there is an increase in pulmonary pressure[2] e.g., during a Valsalva maneuver or strenuous activity[2] but some PFOs are persistently open and believed to be more dangerous since they pose a constant threat for arterializations of gas bubbles (Medical Operations EVA IPT 1999). An autopsy study reported that the overall incidence of PFO in 965 subjects was 27.3% with a median diameter of 5 mm; 9.7% of the subjects had a PFO greater than 5 mm (Hagen 1984). The incidence of resting PFO was reported to be 5 to 10% in the literature and might be as high as 21% in the experience of the JSC Cardiovascular Laboratory (Waligora 1999).

Concern about the role of PFO in the development of decompression sickness arose from diving data. Studies have shown that divers with a PFO have a 2.5 to 4.5 fold increase in the risk of developing type II DCS (Bove 1998, Drighil 2007). To date, PFO has been the most studied risk factor of DCS, although its role in altitude exposures remains controversial for a number of reasons, including the lack of a standardized technique for detecting PFOs and uncertainty about the exact incidence of DCS.

PFO Committee/Medical Operations EVA IPT

In 1999, a NASA-sponsored committee was tasked with reviewing data on PFO and making recommendations about the merit of PFO screening in the astronauts and test subjects. The Medical Operations EVA Integrated Product Team □0HG□2SV□(9$□,37□□VXEVHTXHQWO\□UHYLHZHG□WKH□FRPP recommendations and consulted outside experts to develop a consensus position on PFO screening.

Despite the strength of evidence in diving exposures, PFO had not been directly linked to Type II DCS in altitude exposures. A retrospective study by the Navy found no association between PFO and Type II DCS in 45 aviators who presented with Type II DCS symptoms related to altitude physiological training (Gallagher 1996).

In an Air Force altitude chamber-based study in which 1,500 volunteer subjects were monitored for gas emboli simultaneously in the right and left sides of the heart at simulated altitude, six subjects were found to have right-to-left gas crossover; five of these subjects were symptomatic with joint pain or skin mottling (but no cerebral symptoms) at the time of arterial gas embolism. Of the six cases, one was found to have a PFO, one had a small sinus venosus defect, three had no septal defect, and one was not available for evaluation (Pilmanis 1996). In another presentation, Pilmanis reported 39 cases of Type II DCS in over 2000 research exposures simulating EVA exposures of 4-hour durations or longer, and none of these subjects had detectable gas phase crossover during Trans Thoracic Echocardiography (TTE) monitoring of all four cardiac chambers.

While no published study showed a statistically significant association between PFO and Type II DCS in altitude exposures, case reports did suggest a relationship. Past hypobaric chamber research at JSC identified five cases of Type II DCS. Three of these cases were tested: two (66%) were found to have a

PFO. Of note, four of the five cases did not prebreathe oxygen. A serious case of Type II DCS was reported at Duke University during Phase III testing of the Prebreathe Reduction Program, despite two hours of oxygen prebreathe and albeit a less conservative nitrogen elimination protocol than the ISS operational protocol. This subject was later determined to have a resting PFO.

Based on the available data, the PFO Committee recommended screening all individuals for high-risk PFO, such as resting PFO, PFO in excess of 5 mm in diameter, or individuals with more than 20 countable bubbles observed passing through the PFO during a measurement. It was noted, however, that some PFOs that opened only with provocation during strenuous EVA might have a greater diameter than a smaller resting PFO. Furthermore, TTE with bubble contrast, the screening technique recommended by the PFO Committee, had a sensitivity of 60 to 70%□□DQG□LGHQWLI\LQJ□³KLJK□UHVLVN□3)2V′□ challenging and somewhat subjective. Transesophageal echocardiography was considered the gold standard but invasive and not without risk.

The Med Ops EVA IPT noted that PFO screening could potentially eliminate 10 to 25% of EVA-proficient crewmembers from the existing cadre of astronauts and severely limit the operational flexibility of assigning crewmembers to station missions. Furthermore, given the limitations of PFO screening as well as the unclear relationship between PFO and Type II DCS in altitude exposures, PFO screening would not eliminate the risk of Type II DCS on orbit. A more effective means of mitigating the risk of Type II DCS would be to minimize the chance of bubble formation by oxygen prebreathe procedures.

Taking tKH□3)2□&RPPLWWHH¶V□UHFRPPHQGDWLRQV□into account, the Med Ops EVA IPT recommended the following:

1. That NASA continue to eliminate astronaut candidates with flow-significant atrial septal defects detected with TTE.
2. That an in-suit Doppler be implemented as soon as possible, and that an on-orbit operational validation of the 2-hour prebreathe protocol be conducted.
3. That a multi-center retrospective study be initiated to determine the association between PFO and Type II DCS in well-controlled altitude exposures, as a function of decompression stress.
4. That other prospective PFO studies be considered for funding.
5. That the possibility of screening out astronauts for high risk PFO continue to be considered as warranted by new data or diagnostic modalities.
6. That sensitive screening methods for the risk of Type II DCS be developed, beyond screening for PFO, i.e., screening for a combination of PFO and the propensity to produce high-grade venous gas embolism, which would occur in a very small percentage of astronauts.

Beyond the Med Ops EVA IPT Report

Since 1999, other retrospective studies and meta-analyses have supported the relationship between PFO and Type II DCS in divers. In a retrospective cohort study of 52 sport divers, Schwerzmann et al. (2001) found a 4.5-fold increased risk for DCS in divers with PFO than those without a PFO. On MRI, almost twice as many ischemic brain lesions were seen in divers with PFO, but the difference was not statistically significant. The authors did not analyze the relationship between these brain lesions and

DCS. Gempp et al. (2009) studied 49 divers with spinal cord DCS and found that divers with DCS were 3.6 times more likely than healthy divers to have a large right-to-left shunt on transcranial Doppler ultrasonography; while shunting was not associated with an increased incidence of cervical spinal cord DCS, divers with a right-to-left shunt were 6.9 times more likely to have thoracolumbar DCS. These studies confirm the increased prevalence of PFO or right-to-left shunting in divers who experience DCS and begin to offer a neuropathological basis for symptoms seen in Type II DCS.

New data also suggest that PFOs evolve as divers age. Anecdotally, some divers suddenly become susceptible to DCS after an uneventful diving career of many years. A longitudinal study spanning 6 to 8 years found that the permeability of the foramen ovale in 40 divers changed; while 7.5% of the divers who initially had a PFO saw closure of the PFO, 22.5% of the study cohort developed increased permeability, half of whom had no initial PFO (Germonpré 2005).

In altitude exposures, it remains unclear whether PFO is a risk factor for Type II DCS. An evidence-based literature review concluded that PFO could occur in altitude-induced DCS, but there was no information beyond two case series to indicate causality (Straus 2001). Under-reporting of symptoms in altitude conditions due to perceived negative career impact might partly explain the paucity of data.

It has been suggested that diving and altitude exposures are fundamentally different entities, as evidenced by the observation that the most common symptoms of DCS at altitude are pain only, as opposed to neurologic symptoms seen in recreational divers (Moon 2000); moreover, DCS symptoms tend to occur during altitude exposure versus after diving exposure (Pilmanis 2004). Differences in duration of exposure, prebreathe protocols, and oxygen use during exposure, as in the case of EVA, may further account for the difference in diving and altitude data. Review of the literature since 1999 reveals that additional research is needed to ascertain the relationship between PFO and Type II DCS in altitude exposures. Thus, the benefit of screening astronauts for PFO remains unclear.

OTHER FACTORS AFFECTING INDIVIDUAL SUSCEPTIBILITY TO DCS

While patent foramen ovale has been studied the most, other risk factors for DCS have been proposed based on known mechanisms, including bubble crossover through the heart, bubble crossover through the lungs, and autochthonous bubbles. PFO and right-to-left shunting represent only the first mechanism. Little is known about conditions that allow crossover through the lungs, which appear to have a threshold for filtration of venous bubbles by the pulmonary vasculature, at least in dogs (Butler 1985). A variety of individual parameters and environmental factors have been studied in an effort to identify risk factors for autochthonous bubble formation that lead to susceptibility to DCS.

Individual Parameters

Parameters such as age, height, weight, body mass index, percent body fat, aerobic capacity, and gender have been reported to influence DCS incidence (Sulaiman 1997, Conkin 2003, Webb 2003 and 2005). In the most comprehensive study of these parameters to date, Air Force researchers sought to quantify individual susceptibility to DCS and determine if the aforementioned variables could be used to predict

DCS risk. Retrospectively reviewing 2980 altitude exposures in the Air Force Laboratory Altitude DCS Research Database, Webb et al. (2005) found that the combination of lower VO_{2max} and greater weight appeared to be the best predictor of DCS, but this accounted for less than 13% of the variation in DCS susceptibility. The authors concluded that individual susceptibility to DCS could not be predicted by these anthropometric and physiologic variables.

In another study, Webb et al. (2003) prospectively compared male and female subjects in 961 exposures to simulated altitude and found no statistically significant difference in DCS incidence between men (49.5%) and women (45.3%). Among women, they found no difference in DCS during the first two weeks of the menstrual cycle between users of hormonal contraception vs. non-users. However, if only the last half of the menstrual cycle were considered, hormonal contraception appeared to double the risk of DCS, a finding supporting an earlier report by Doyle et al. (1997) but refuted by Lee et al (2003).

Lee and her colleagues surveyed 240 female sports divers treated with hyperbaric therapy for DCS in 23 treatment centers worldwide, and found the incidence of all DCS symptoms to be greatest in the first half of the menstrual cycle (29 to 34%), with a marked fall in the third week (13 to 23%) before rising again in the fourth week (21 to 25%); the trend was similar for Type I and Type II symptoms. The effect of contraceptive use appeared to shift the occurrence of DCS to later in the cycle but there was no significant difference between contraceptive users and non-users, although a statistically significant difference existed between the two groups when age was taken into account. The observed differences in these studies might have been due to differences in how menstrual history was recorded as well as doses and formulation of contraceptives. More study is needed to draw a conclusion about the role of menstruation and contraceptive use in the risk of DCS in women, and whether EVA schedules would need to be adjusted accordingly.

$Q□LQGLYLGXDO¶V□diving experience has also been linked to DCS risk. In a survey-based study of 429 subjects, Klingmann et al. (2008) found a 2.51-fold higher lifetime incidence of DCI in divers with a history of deep dives greater than 40 meters compared to divers whose lifetime maximal depth was 40 meters or less. The reODWLYH□ULVN□RI□'&6□EHWZHHQ□GLYHUV□ZLWK□□□□□□RU□IHZHU□GLYHV□H[SHULHQFH□GLYers with more than 400 dives was 3.90. Similarly, certification to lower depths was associated with 1.97 to 8.17 times higher incidence of DCS. There was no statistically significant difference between technical divers and non-technical divers. Attrition, rather than any physiologic factors, was identified as the explanation for the association between low-depth diving experience and risk of DCS, but the authors did acknowledge a selection bias in their methodology and called for further study before their results could be generalized to all divers. Similarly, prior DCS might predispose an individual to subsequent development of DCS, but data have been limited to observations of caisson workers in the 1970s (Francis 2003).

On the other hand, a more recent study suggested that repeated scuba dives and regular physical exercise activity might protect against DCS, possibly due to reduced bubble formation (Pontier 2009). However, exercise itself has been observed to offer protection from DCS. In addition to laboratory studies that showed sedentary rats and pigs were more susceptible to severe DCS and death than exercise conditioned groups (Broome 1995, Wisløff 2001), several human studies have found decreased venous gas emboli formation, thereby inferring decreased DCS risk, in divers who exercised 24 hours before diving (Dujiü

2004), 2 hours before diving (Blatteau 2005), during decompression (Jankowski 1997), and during a decompression stop (Dujiü 2005). In altitude exposures, exercise during prebreathe (Gernhardt 2000, Webb 2004) also appeared to be beneficial in preventing DCS.

Biochemically, limited studies have suggested that subjects susceptible to the formation of venous gas emboli during decompression had significant higher levels of total cholesterol, high-density lipoprotein cholesterol, potassium, phosphate, calcium, and magnesium (Jauchem 1986). A follow-on study was unable to replicate these findings, and it was noted that factors such as prebreathe time, use of an intermediate pressure stage, and length of time in the chamber could affect various biochemical parameters (Jauchem 1990).

The observation that many of the effects of complement activation were similar to the symptoms of DCS led to several studies that ultimately disproved complement activation as a risk factor for DCS. Ward et al. (1987) found that the presence of air bubbles in plasma activated the complement system by the alternate pathway and that subjects who were more sensitive to this complement activation were more susceptible to DCS. However, in vivo testing failed to demonstrate this phenomenon and subjects who developed DCS showed no difference in complement activation during dives compared to healthy subjects (Shastri 1997).

Finally, a history of cigarette smoking may predispose an individual to DCS. A retrospective analysis of the Divers Alert Network (DAN) database found that heavy smokers (>15 pack-year history) were 1.88 times more likely to have DCS than divers who had never smoked and 1.56 times more likely than light smokers (0-15 pack-year history) (Buch 2003).

Environmental Factors

Fluid balance appears to play a role in DCS. One study randomized swine subjects into two groups: a hydrated group that was allowed ad lib access to water during a simulated saturation dive, and a dehydrated group that was given intravenous furosemide without access to water. The dehydrated group showed a significantly increased rate and faster onset of DCS and death, possibly due to increased bubble formation or altered nitrogen removal (Fahlman 2006).

Ambient temperature has also been considered as a risk factor for DCS. A Navy study sought to compare the incidence of DCS in divers who were immersed in air decompression dives to 120 feet of seawater at either 97°F or 80°F, and found that warm conditions during bottom time and cold conditions during decompression increased the risk of DCS, but this finding was confounded by dehydration (Gerth 2007). Other studies found that hot water suits were 1.81 to 1.96 times more likely than passive thermal protection to be associated with DCS, although some of these findings might have been attributable to the dive profile or bottom time (Leffler 2001). It has been proposed that increased susceptibility to DCS may result from increased gas uptake in warm conditions and decreased elimination in cold conditions, but there is insufficient data to confirm this theory (Toner 2004).

CONCLUSION

The ability to predict an individual's susceptibility to decompression sickness in hypobaric environments would be advantageous for astronaut selection, crew assignment, and mission planning. To date, much focus has been on PFO as a risk factor for DCS, but a number of other individual parameters as well as environmental factors have also been implicated in increased risk of DCS. Although diving exposures were once considered analogous to altitude exposures, there is increasing appreciation for the fundamental differences between diving and altitude. There continues to be a need for altitude research under controlled conditions to evaluate potential risk factors for DCS in altitude exposures and apply knowledge about individual susceptibilities to mission planning. In the meantime, it seems sensible to continue current protective measures such as exercise-enhanced prebreathe periods to minimize the risk of DCS in hypobaric environments.

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