Partial Pressure of Nitrogen in Breathing Mixtures and Risk of Altitude Decompression Sickness

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Background: Many aircraft oxygen systems do not deliver 100% O_2. Inert gases can be present at various levels. The purpose of this study was to determine the effect of these inert gas levels on decompression sickness (DCS). ***Methods:*** Subjects were exposed for 4 h to 5486 m (18,000 ft) with zero prebreathe, using either mild (Test A) or strenuous exercise (Test B), and breathing 60%N_2/40%O_2. Test C used a breathing mixture of 40%N_2/60%O_2 at 6858 m (22,500 ft) with zero prebreathe and mild exercise. Test D investigated a breathing mixture of 2.8%N_2/4.2%argon/93%O_2 with 4 h exposures to 7620 m (25,000 ft), mild exercise, and 90 min of preoxygenation. The controls were from previous studies using similar conditions and 100% O_2. ***Results:*** The DCS risk for Tests A and B and the Control for B was 7%; the Control for Test A was 0% (n.s.). Breathing the 40%N_2/60%O_2 mixture (Test C) resulted in 43% DCS compared with 53% DCS with 100% O_2 (n.s.). When the 2.8%N_2/4.2%argon/93%O_2 mixture was used, the results showed 25% DCS compared with 31% DCS with 100% O_2 (n.s.). ***Conclusions:*** The increased nitrogen and argon levels in the breathing gas while at altitudes of 5486 m to 7620 m did not increase DCS risk. These results support the concept of using the partial pressure gradient of inert gases instead of the percentage of N_2 or argon in a breathing gas mixture to determine the risk of DCS during altitude exposure.

Keywords: altitude, venous gas emboli, on-board oxygen generating systems, argon, decompression sickness, nitrogen, breathing gas.

ALTITUDE DECOMPRESSION sickness (DCS) can occur when personnel are decompressed to a combination of altitudes and exposure times sufficient to elicit evolved gas (primarily nitrogen) in the tissues. Bubble formation in the body can result in DCS symptoms ranging from mild pain to serious neurological/respiratory impairment. For aerospace exposures above 5486 m (18,000 ft), if cabin pressurization is not possible, the primary countermeasure is preoxygenation (prebreathing). This procedure consists of breathing 100% oxygen for some period of time prior to and during ascent to altitude. By breathing 100% O_2 there is zero nitrogen in the inspired breathing gas, creating the maximum driving force for nitrogen elimination from the body (denitrogenation). Continuing to breathe 100% O_2 during the altitude exposure further reduces the N_2 in the tissues, as well as preventing hypoxia.

The extent of denitrogenation varies primarily with breathing gas mixture, altitude, time of exposure, prebreathe time, and changes in circulation (e.g., exercise, thermal stress). The differential set up by these variables between the partial pressure of N_2 in the tissues and the partial pressure of N_2 in the ambient breathing gas can be referred to as the nitrogen partial pressure gradient or the P_{N_2} gradient. As mentioned above, the exclusion of nitrogen in the breathing gas, i.e., preoxygenation with 100% oxygen, maximizes the P_{N_2} gradient. Therefore, it is generally accepted that the more N_2 in the breathing gas the less effective the denitrogenation, and the higher the risk of DCS. This may be correct for preoxygenation at ground level. However, there is only limited evidence to support this concept during altitude exposure.

Barer et al. (1) found that greater than 10% N_2 during prebreathing at ground level nullified the denitrogenation effect. An Air Force Research Laboratory (AFRL) study on the effects of breathing a 50% nitrogen/50% oxygen mixture at 5929 m (16,500 ft) showed significantly more circulating venous gas emboli while breathing the 50/50 mix than with the use of 100% O_2 (10). Unfortunately, the latter study was done at low altitudes and measured only circulating gas emboli, since DCS did not occur. Work at higher altitudes with mixed gas breathing has not been documented, and, therefore, the effect of high N_2 breathing mixtures on the DCS risk at altitude is not well understood.

Oxygen systems in military aircraft using the USAF Narrow Panel Regulator have two regulator settings: 100% O_2 and Normal. The Normal setting prevents hypoxia by diluting the air with O_2 at the lower altitude, thereby reducing consumption of aircraft O_2 stores and reducing the potential for pulmonary acceleration atelectasis. For example, at 5486 m, the minimum O_2 concentration is approximately 38% when using this system. At 7620 m, the minimum O_2 concentration is 52% and reaches 100% at approximately 10,059 m (33,000 ft). Thus, it is of interest to determine if these high levels of N_2 in the breathing gas significantly contribute to DCS risk, particularly in unpressurized aircraft.

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Currently, most military aircraft are replacing the liquid oxygen and high-pressure gas systems with On-Board Oxygen Generating Systems (OBOGS). This molecular sieve oxygen concentrator technology is used for generating oxygen-enriched breathing gas to prevent hypoxia in unpressurized aircraft and pressurized high altitude aircraft. OBOGS does not generate 100% O_2. A number of parameters such as altitude, number of people breathing on the system, level of activity of the crew, supply of air, temperature, and others, determine the exact make-up of the OBOGS product gas. Under some conditions, the N_2 concentration can reach as high as 40% at 5486 m. Under the "best" conditions, OBOGS product gas concentrations running near optimal performance can be 93.0% O_2, 4.2% argon; and 2.8% N_2. This is the highest O_2 concentration OBOGS can deliver. For example, the highest percent oxygen level that can be obtained in the OBOGS product gas of the unpressurized tiltrotor CV-22 Osprey aircraft with a crew of four at 5486 m (18,000 ft) is approximately 82%.

As noted above, the OBOGS product gas also contains another inert gas, argon. Argon (Ar) has lower diffusivity than nitrogen, but a higher solubility in fatty tissue. Thus, breathing high levels of Ar could result in higher DCS risk than breathing the same concentration of N_2. However, if the Ar concentration is low and exposure time short, its impact on bubble growth and DCS risk should be minimal. Cooke et al. (3) studied the effect of Ar on DCS but reported results that were inconclusive. A recent study in our lab found an increase in DCS when an Ar/O_2 mixture was breathed for 4 h at 5486 m just prior to ascending to 10,668 m (35,000 ft) for 3 h (6). However, the Ar concentration in the breathing gas of that study was much higher (62%) than that found in OBOGS product gas. Thus, the impact of Ar on DCS risk when using OBOGS is not known.

Aircraft oxygen systems deliver breathing gases with varying amounts of N_2, and it is generally assumed that breathing high levels of N_2 will result in slower denitrogenation and a higher risk of DCS than breathing 100% oxygen. Data were needed to define the effect of increasing levels of N_2 in the breathing gas on the DCS incidence during altitude exposures at 5486 m and above. Further, the impact of argon, albeit small, from OBOGS on the DCS risk also needed definition. As altitude increases (total ambient pressure decreases), the P_{N_2} gradient from the tissues to the air being breathed by a crewmember also increases due to the lower partial pressure of N_2 in the air at altitude. This study tested the hypothesis that the increasing P_{N_2} gradient between the ground-level tissue N_2 saturation and the ambient P_{N_2} at and above 5486 m does not increase DCS risk while breathing high percentages of N_2 when compared with the DCS risk found while breathing 100% O_2. In addition, we hypothesized that the small amount of argon from the OBOGS product gas would have no impact on the DCS risk.

METHODS

The voluntary, fully informed consent of the subjects used in this research was obtained, and the protocols were approved by an Institutional Review Board. All subjects passed an appropriate physical examination and were representative of the USAF rated aircrew population. They were not allowed to participate in scuba diving, hyperbaric exposures, or flying for at least 48 h before each scheduled altitude exposure. Prior to each altitude exposure, a physician conducted a short physical examination of subjects to identify any signs of illness or other problem that would endanger the subject or bias the experimental results. Chamber ascent and descent were at a rate not exceeding 5000 fpm. A neck-seal respirator made by Intertechnique® (Plaisir Cedex, France) was used to deliver the breathing gas. This mask provided a slight (2 cm of water) positive pressure which reduced the opportunity for inboard leaks of air from the atmosphere and was more comfortable than the standard aviator's mask.

At 15-min intervals, the subjects were monitored for venous gas emboli (VGE) using a Hewlett Packard® SONOS 1000 Doppler/Echo-Imaging System (Palo Alto, CA). This system permits both audio and visual monitoring and recording of gas emboli in all four chambers of the heart. The monitoring periods lasted approximately 1–2 min each and included five recorded VGE scores. The "general" VGE score was taken with the subject at rest. A VGE score was then taken, in turn, as each limb was flexed and rotated twice. A 5-point VGE grading scale similar to the Spencer Scale (9) was used. Each VGE score was an average during the monitoring period. This method is considered to be semi-quantitative, recognizing that the precise number of bubbles in a heart cycle is difficult to score, the number varies from cycle to cycle in a monitoring period, the same bubbles may be counted more than once, etc. The grades were defined as follows: Grade 0 = no bubble signals; Grade 1 = occasional bubble signals; Grade 2 = frequent bubble signals; and Grade 3 = many bubble signals, but they do not obscure the heart sounds. Mild exercise consisting of three upper-body exercises as described in Webb et al. (11) was performed by the subjects at intervals throughout the altitude exposure. The subjects walked less than 10 steps between exercise stations and the echo-imaging station at 4-min intervals.

AFRL medical monitors insured subject health and safety, and made the diagnosis of DCS. Subjects were alone in the chamber while at simulated altitude. The echo imaging transducer was placed using a robotic arm operated from outside the chamber. The subjects were instructed to report any changes in well-being to the medical monitor and the determination to terminate the exposure was made from these reports. The subjects were examined after recompression to ground level. The medical monitors were trained in the diagnosis of DCS, and had the ability to consult with the physicians in Hyperbaric Medicine within the same building. Endpoints of the exposures were: 1) completion of the scheduled exposure period; 2) diagnosis of DCS; or 3) detection of left ventricular gas emboli. A more detailed description of the endpoints can be found elsewhere (7).

Subjects were not questioned about how they felt during the altitude exposures. To provide relief from boredom and more closely emulate operational distractions, movies were shown to the subjects during the

TABLE I. EXPERIMENTAL EXPOSURES.

	Test A	Test B	Test C	Test D
# of Subjects in Tests	30	29	40	40
# of Subjects in Controls	20	30	40	ADRAC
Altitude (m)	5486	5486	6858	7620
P_{N_2} (mmHg)	228	228	126	8
N_2 Gradient (mmHg)	355	355	457	575
Gas Mixture	60%N_2/40% O_2	60%N_2/40% O_2	40% N_2/60% O_2	2.8%N_2/4.2%Ar/93%O_2
Prebreathe (min)	N/A	N/A	N/A	90
Activity	mild exercise	heavy exercise	mild exercise	mild exercise

hypobaric exposures. The subjects received a briefing on the morning of each exposure which emphasized their responsibility to report any DCS symptoms or change in well-being to chamber personnel, and a list of symptoms was posted in plain view inside the chamber. The significance of the response, DCS or no DCS, of subjects was analyzed using the Chi-squared test. Log Rank and Wilcoxon's tests were used to compare homogeneity of curves representing cumulative incidence of DCS and VGE vs. time.

Four experimental altitude exposure profiles were used to determine the effect of high levels of N_2 in the breathing gas on DCS risk while at altitude. The details of the profiles of Tests A and B are in **Table I**. In Test A (n = 30), the subjects performed mild exercise as described in Webb et al. (12). Test B was identical to Test A except heavy exercise (dual cycle ergometry at 50% $\dot{V}O_{2peak}$) was used at altitude (n = 29). The controls for these two tests using similar conditions but 100% O_2 for a breathing gas had previously been accomplished in our lab and the data were available in the Air Force Research Laboratory (AFRL) DCS Research Database.

Table I also describes the conditions of Test C and D. Test D was used to determine the effect of the optimum OBOGS breathing gas, including argon, on DCS risk. In Test D, the breathing gas used during both the preoxygenation period and during the altitude exposure was 93% oxygen, 4.2% argon, and 2.8% nitrogen, representing the highest oxygen level generated by most OBOGS systems.

The control for Test C using similar conditions but 100% O_2 for a breathing gas had previously been accomplished in our lab and the data were available in the AFRL Altitude DCS Research Database. However, no such control for Test D was available in the database. Therefore, the control for Test D was generated by a DCS risk prediction model developed at AFRL. This Altitude DCS Risk Assessment Computer (ADRAC) model is based on loglogistic distribution and bubble growth. It is used to predict the probability of DCS over time as a function of altitude, preoxygenation time, exposure time, exercise, and the time of onset of maximum venous gas emboli grade. A prospective series of human trials successfully validated the predictive ability and accuracy of this model. A detailed description of the ADRAC model can be found elsewhere (8).

RESULTS

A total of 139 subject-exposures were completed by 55 subjects. Of these subjects, 10 completed only one exposure, 14 completed 2 exposures, 23 completed 3 exposures, and 8 completed all 4 exposure profiles. Since many of the subjects completed multiple profiles, it is not surprising that the anthropometric data of the four profiles are very similar. The mean values (SD) for the four profiles combined were: weight 81.5 kg (1.6); height 175.4 m (0.8); Body Mass Index 26.4 (0.2); fat content 17.5% (0.4); $\dot{V}O_2$ max 3.3 L · min^{-1} (0.1); and age 31.1 yr (0.5).

At the end of the 4-h exposures to 5486 m with zero prebreathe and mild exercise while breathing 60%N_2/40%O_2 (Test A), the cumulative DCS incidence was 7% (**Table II**). The DCS incidence with the control expo-

TABLE II. DCS AND VGE RESULTS.

	Test A	Test B	Test C	Test D
DCS				
Controls	0%	7%	50%	31% (ADRAC)
DCS Incidence	7%	7%	43%	25%
Chi-squared	0.20	0.23	0.80	
p	0.66	0.63	0.37	
VGE				
Controls	30%	63%	63%	N/A
VGE Incidence	70%	69%	90%	50%
Chi-squared	7.73	0.21	6.9	—
p	0.01*	0.65	0.01*	—
VGE Grade 4				
Controls	10%	23%	23%	N/A
VGE Grade 4 Incidence	27%	17%	38%	20%
Chi-squared	1.17	0.34	2.14	—
p	0.28	0.56	0.14	—

* = significant

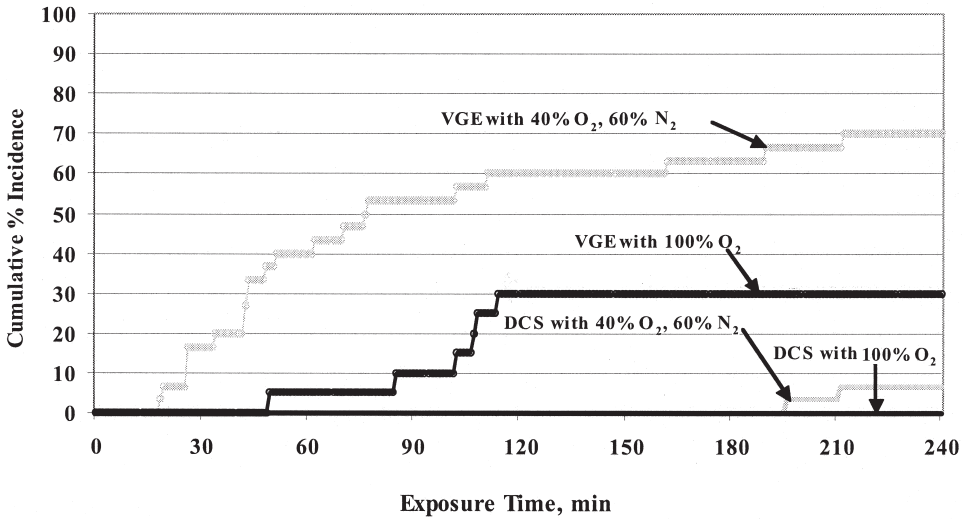

Fig. 1. Cumulative % incidence of DCS and VGE at 5486 m; mild exercise; 240-min exposure; no preoxygenation (Test A).

sures breathing 100% O_2 was 0%. This difference was not significant. However, there was a significant difference between the VGE incidence of Test A and the control values (70% vs. 30%). There was no significant difference for Grade 4 VGE. **Fig. 1** shows the Test A cumulative onset curves for DCS and VGE. Here again, the difference between the test and the control VGE values is clear. The Test B profile was identical to that of Test A except it had heavy exercise instead of mild exercise. The cumulative DCS incidence at the end of the Test B exposures was 7% for both the test and the control exposures (Table II). Unlike Test A, however, there was no significant difference between the test and control cumulative VGE incidence or Grade 4 VGE in Test B (**Fig. 2**).

Results from Test C (at 22,500 ft breathing a mixture of 40%N_2/60%O_2, with zero prebreathe and mild exercise) showed that there was no significant difference between the test and the control in cumulative DCS incidence, but there was a very significant difference in the cumulative VGE incidence (Table II, **Fig. 3**). However, there was no such difference for Grade 4 VGE. Table II also contains the results from Test D (at 7620 m breathing an OBOGS mixture with 90 min of prebreathe). Since there was no control available in the AFRL DCS Database for Test D, the only control value available was obtained from the ADRAC model. However, statistical comparison is not possible when the control value is generated by a predictive model. Since ADRAC does not predict VGE values, there was no control for the VGE incidence. **Fig. 4** shows the cumulative DCS and VGE onset curves for Test D. The dotted line represents the DCS risk predicted by ADRAC for this exposure profile.

DISCUSSION

Percentage is the most common way of referring to the components of a breathing gas mixture an aviator is receiving. However, for defining DCS risk, the results of this study indicate that percentage of N_2 is not the most useful term. The total pressure of a breathing gas mixture is made up of the partial pressure components of that mixture (O_2, N_2, Ar). In the aerospace setting, if the

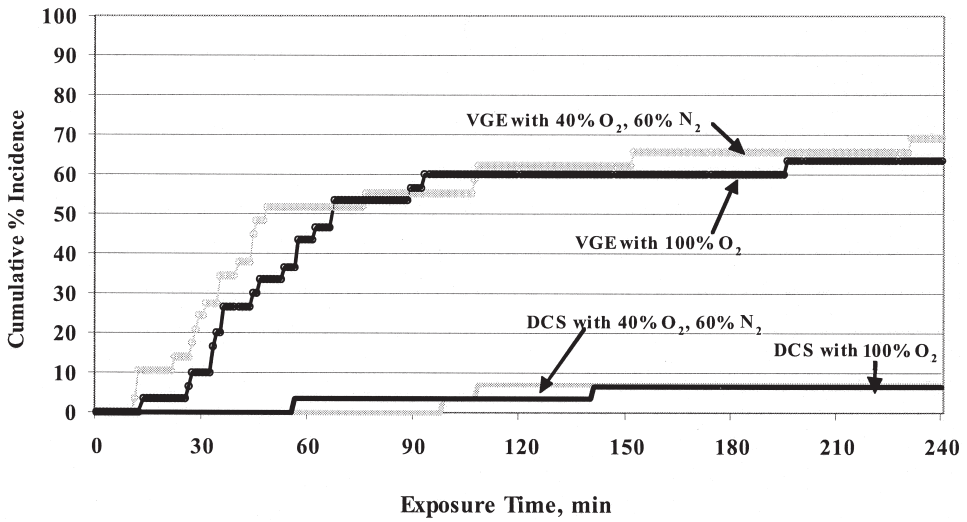

Fig. 2. Cumulative % incidence of DCS and VGE at 5486 m; heavy exercise; 240-min exposure; no preoxygenation (Test B).

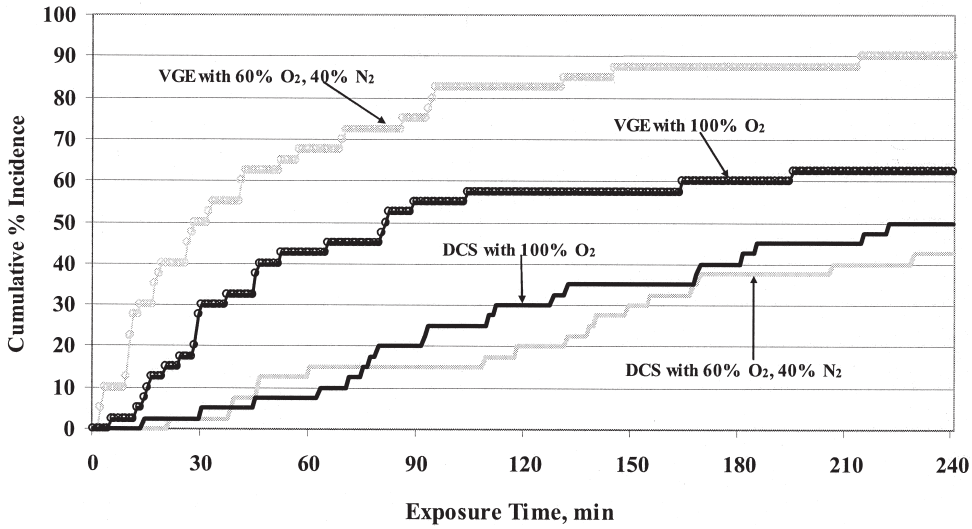

Fig. 3. Cumulative % incidence of DCS and VGE at 6858 m; mild exercise; 240-min exposure; no preoxygenation, 40% N_2/60% O_2 (Test C).

percentage of each of those individual gases stays constant as altitude increases (pressure decreases), the partial pressures of each of those gases will obviously decrease. Assuming that with exposure to altitude the partial pressure of N_2 in the "slow" tissues (minimally perfused tissues slow to give up N_2) in the body remains initially at ground-level saturation concentration, the P_{N_2} gradient (the difference between the partial pressure of N_2 in the tissues and the partial pressure of N_2 in the ambient breathing gas) will increase. The resulting increased driving force for N_2 to diffuse out of the body will likely decrease the tissue partial pressure of N_2, decrease the potential for bubble formation, and decrease the risk of DCS. The driving force obviously is the greatest if the breathing gas is 100% O_2.

The results of Tests A, B, C, and D showed that the DCS risk at 5486 m, 6858 m, and 7620 m is not increased by breathing gas mixtures containing up to 60% N_2 when compared with breathing 100% O_2. In Tests A and B at 5486 m, the DCS incidence was low, as expected, and it could be said that at such low DCS levels a statistical difference would be hard to find. However, Test C at 6858 m also did not show any significant change in DCS incidence as compared with the control. In Test D, since the N_2 and Ar percentages were very low, and the altitude was even higher, it is not surprising that there was no significant difference in DCS when compared with the use of 100% O_2. Lee and Hay (4), in a similar study, found that there was no significant difference in DCS between breathing 100% O_2 and breathing a mixture of 63% O_2, balance N_2. Their subjects were exposed to 7620 m (282 mmHg) for 4 h at rest after 1 h of 100% O_2 prebreathing at ground level.

While the DCS risk was not different with levels of N_2 between 40% and 60%, the VGE incidence results showed significant differences in Tests A and C. However, in Test B, with strenuous exercise, the VGE incidence was not different from the control. Significant VGE differences between high N_2 breathing mixtures and 100% O_2 (Fig. 1) agree with our previous research

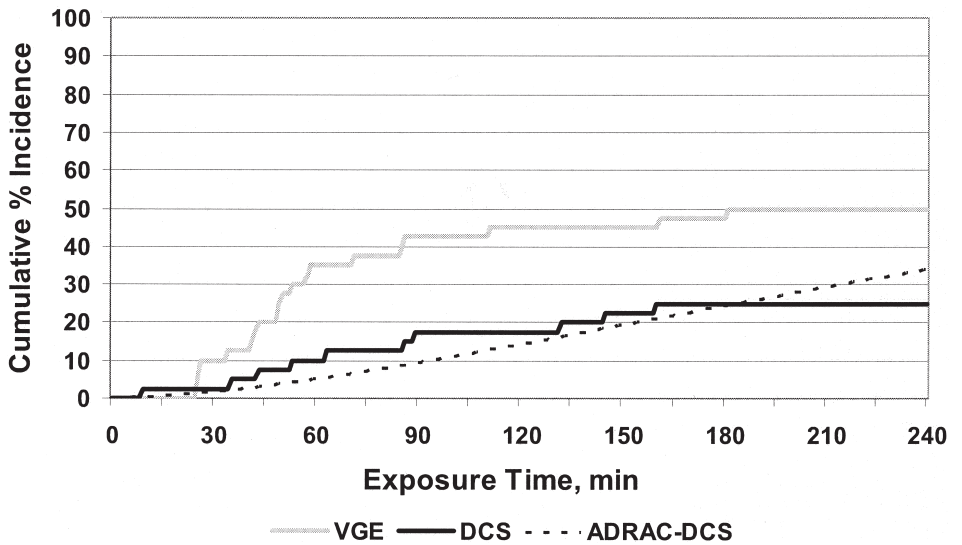

Fig. 4. Cumulative % incidence of DCS and VGE at 7620 m; mild exercise; 240-min exposure; 90-min preoxygenation, 2.8%N_2/4.2%Ar/93%O_2 (Test D). ADRAC = Altitude DCS Risk Assessment Computer Model.

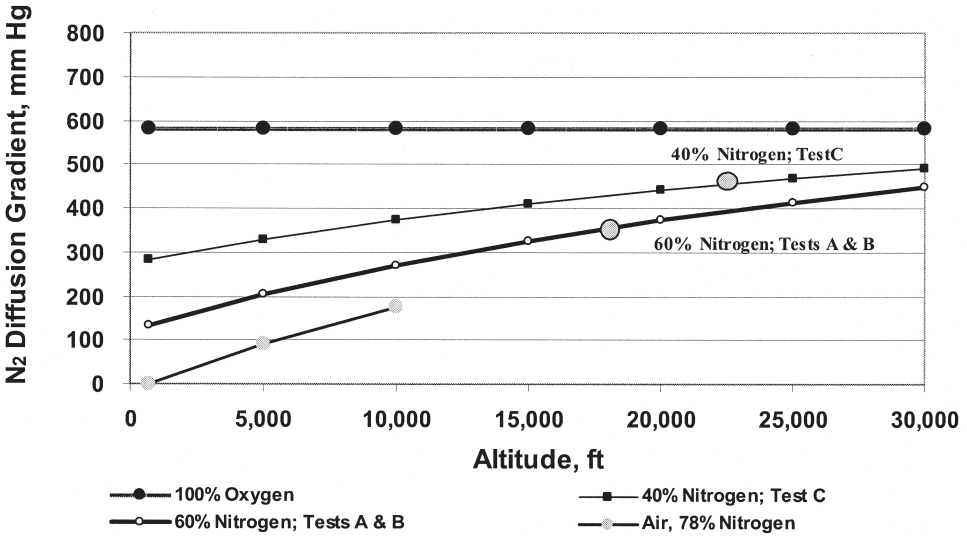

Fig. 5. Calculated P_{N_2} gradient vs. altitude.

(10) and with the results of Lee and Hay (4). The VGE results in Test B (Fig. 2) are contrary to these findings and are difficult to explain. It appears that no matter which gas was used, the heavy exercise results in high levels of VGE. Operationally, since VGE results are not good predictors of DCS symptoms (2,5), these VGE results have little application. However, the VGE results do suggest that there may be some physiological decompression stress increase associated with the higher levels of N_2 in the breathing gas at altitudes above 5486 m (380 mmHg).

The results of this research do not support the widely held view that high percentages of N_2 are likely to increase DCS risk when breathed at high altitude. These results support our hypothesis that it is primarily the P_{N_2} gradient increasing with altitude that determines the level of DCS risk, rather than the percentage of N_2 per se. This effect is illustrated in **Fig. 5**.

At ground level, breathing air, there is no P_{N_2} gradient. The tissues of the body are saturated with ground level N_2 and are at an equilibrium. As an individual ascends in altitude and continues to breathe air, the gradient increases and denitrogenation begins. The plot stops at 3048 m (10,000 ft) because, as a practical matter, the USAF requires the use of supplemental oxygen above 3048 m for hypoxia protection. The other extreme of the gradient spectrum is when 100% O_2 is the breathing gas and the gradient is at a maximum. This maximum does not change with altitude. It cannot get higher than a 583-mmHg differential. Thus, denitrogenation is at its maximum when breathing 100% O_2 whether prebreathing at ground level or flying at 6096 m (20,000 ft). A family of curves for the P_{N_2} gradient and altitude can be plotted for the various breathing gas mixtures between 21% and 100% O_2.

In Fig. 5, the curves for the gas mixtures in Tests A, B, and C are represented. It is clear from this figure that even though the breathing mixture contained 40% or 60% N_2, the denitrogenation was relatively high when at 6858 m. At the exposure altitudes of this study, it appears that the denitrogenation was sufficiently efficient compared with denitrogenation with 100% O_2 that the DCS risk was not significantly different. This concept permeates through all phases of this study and explains the results which are, seemingly, contradictory to conventional wisdom.

The DCS incidence results of Tests A and B both show that there was no significant difference between the use of 60% nitrogen in the breathing gas and 100% oxygen (Table II, Figs. 1 & 2). Thus, these data suggest that the use of the Normal setting on the narrow panel regulators would not result in a greater risk of DCS than using the 100% O_2 setting when operating at 5486 m. By use of the Normal setting, the aircraft oxygen supply would last longer and additional oxygen may not be required for extended flight times.

As with the results of Test A and B, Test C results show that a high level of nitrogen (40%) in the breathing gas does not result in an increased DCS risk (Table II, Fig. 3). The OBOGS of the unpressurized CV-22 aircraft can produce breathing gas with as much as 40% N_2 at 6858 m. The results indicate that, under the conditions of this test, DCS symptom risk would not increase when compared with breathing 100% O_2. Thus, as long as the OBOGS oxygen level is enough to prevent hypoxia, DCS risk will not be significantly higher than if using 100% O_2 from liquid oxygen or high-pressure cylinders. It becomes obvious that Test D was superfluous, since if 40% N_2 does not increase DCS risk, then 2.8% N_2 certainly will not. The were no control exposures in the database to compare the results of Test D to, so the ADRAC model was used to predict the DCS risk. No statistics are possible when comparing to the results of a model prediction, but the results appear similar. Both Tests C and D, and the Lee and Hay study, indicate that the CV-22 OBOGS product gas when used above 5486 m will not impact DCS risk.

CONCLUSION

The nitrogen partial pressure gradient partly determines the extent and rate of denitrogenation during altitude exposure. The degree of denitrogenation, in turn, determines the potential for bubble formation and

DCS incidence. Within the parameters of the experiments of this study, it is concluded that increased nitrogen levels in the breathing gas while at altitudes of 5486 m to 7620 m did not significantly increase DCS risk. Although it is likely that there is greater denitrogenation when using 100% O_2 vs. using a high N_2 mix at these altitudes, as reflected in the increased VGE incidence with high N_2 breathing gases, apparently the magnitude of that difference is not enough to impact the risk of clinical DCS.

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