Evolution and Preservation of Venous Gas Emboli at Alternating High and Moderate Altitude Exposures

Rickard Ånell; Mikael Grönkvist; Mikael Gennser; Ola Eiken

INTRODUCTION: The evolution and preservation of venous gas emboli (VGE), as markers of decompression stress, were investigated during alternating high- and moderate altitude exposures, thus, simulating a fighter aircraft high-altitude flight, interrupted by refueling excursions to lower altitudes.

METHODS: Eight men served as subjects during three normoxic simulated altitude exposures: High = 90 min at 24,000 ft; High-Low = three × 30 min at 24,000 ft, interspersed by two 30-min intervals at 15,000 ft; Low = 90 min at 15,000 ft. VGE scores were assessed by cardiac ultrasound, using a 5-grade scale. Respiratory nitrogen exchange was measured continuously using a modified closed-circuit electronic rebreather.

RESULTS: Both High and High-Low induced persistent VGE, with no inter-condition difference either at rest [median (range): High: 1 (0-3), High-Low: 2 (0-3)] or during unloaded knee-bends [High: 3 (1-4), High-Low: 3 (0-4)], whereas VGE was considerably less in Low, both at rest [0 (0-1)] and during knee-bends [0 (0-2)]. In High-Low, VGE decreased temporarily during the 15,000-ft excursions, but resumed pre-excursion values upon return to 24,000 ft. During the final descent to ground level, VGE were more persistent following High-Low than High. In both High and Low, nitrogen was continuously washed out at altitude, whereas in High-Low, the washout at 24,000 ft was interrupted by nitrogen uptake at 15,000 ft.

DISCUSSION: In normoxic conditions, long-duration flying at a cabin altitude of 24,000 ft is associated with substantial VGE occurrence, which is not abolished by intermittent excursions to a cabin altitude of 15,000 ft.

KEYWORDS: decompression sickness risk, fighter aircraft, gas bubble formation, VGE, hypobaric DCS, in-air refuelling, nitrogen elimination, repeated altitude decompression.

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Altitude decompression sickness (DCS), which may occur upon a prompt and sustained exposure to high altitude, is caused by supersaturation of physically dissolved gas and consequent formation of bubbles in blood and other tissues (for review see Stepanek and Webb[22]). DCS remains a problem in military aviation, mainly because military aircraft commonly need to operate at high altitude, and since, during such sorties, the aircraft cabin pressure must be kept low to reduce the risk of pulmonary barotrauma in case of sudden, accidental cabin decompression.[12] In modern fighter aircraft, the cumulated flying time at low cabin pressures may be substantial even during a single sortie, since the planes typically have in-flight refueling capacity, permitting prolonged high-altitude flying interrupted by excursions to lower altitude for refueling.

It is well documented that the risk of DCS increases with the exposure duration during acute, sustained exposure at high altitude,[27] whereas information is scarce and inconclusive regarding DCS risk in conjunction with repeated high-altitude exposures. It can be assumed that reasons for the equivocal risk assessments for repeated high-altitude exposures, ranging from increased[8] to decreased[21] DCS risk compared to that during a sole high-altitude exposure, include variations in the magnitude and duration of the intermittent recompressions.[32] Thus, it appears that during long-term exposure to cabin altitudes of

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24,000–25,000 ft,[20,32] the pressure increase induced by an excursion to 900 ft is of sufficient magnitude to induce substantial and permanent compression of the venous gas emboli (VGE) formed at high altitude. By contrast, repeated altitude excursions from 24,000 ft to 20,000 ft appear to increase the occurrence of VGE at 24,000 ft,[32] presumably because the pressure increase during such excursions is not sufficient to compress VGE below a collapse radius, and that eventually the excursions might instead act to replenish the tissue nitrogen (N_2) depots. In addition, acute exposure to 20,000 ft may per se induce VGE, and hence continued formation of VGE during the initial excursion to 20,000 ft may have contributed to the high prevalence of VGE during the subsequent exposure to 24,000 ft.[32]

The aim of the present study was to investigate the evolution and preservation of VGE during alternating normoxic exposures to an altitude likely to induce VGE (24,000 ft) and an altitude unlikely to per se induce VGE (15,000 ft); the choice of 15,000 ft as the excursion altitude was also dictated by operational considerations, namely that it constitutes a low yet realistic cabin altitude for in-flight refueling of a modern fighter aircraft. In addition to the alternating 24,000 and 15,000 ft trial, control trials were performed at sustained exposure to 15,000 and 24,000 ft, respectively. Decompression stress was evaluated by determination of VGE and of whole-body washout and uptake of N_2.

METHODS

Subjects

Eight healthy men, with mean (range) age and body mass index (BMI) of 44 (27–54) yr and 29.2 (24.6–34.1) $kg \cdot m^{-2}$, respectively, participated as test subjects. They were recruited among fighter pilots ($N = 2$), divers ($N = 5$), and military altitude operators ($N = 1$). Only one of the subjects had experienced decompression sickness (DCS) earlier, but all were well informed of DCS symptoms and all were familiar with pressure-chamber exposures. None of the subjects were smokers and all had passed their annual physical and medical assessment prior to the study. The subjects gave their written, informed consent prior to enrolling, and had been apprised that they were free to prematurely terminate any single experiment, or to withdraw from the study at any time. The study was approved by the regional Human Ethics Committee in Stockholm, Sweden (approval no: 2017/1451-31) and conformed to the Helsinki Declaration.

Equipment

A four-chamber view of the heart was monitored using an ultrasound system (CX50, Philips Ultrasound, Bothell, WA, USA) equipped with a 1 – 5 MHz linear-array transducer (S5-1). Cardiac impedance measurements were performed using an electric impedance cardiography system (Physioflow PF07, Enduro, Manatec Biomedical, Paris, France). Capillary oxyhemoglobin saturation (S_pO_2) was measured using a pulse oximeter (Radical 7 monitor, MASIMO SET, Rainbow, CA, USA). The closed rebreather used was a Poseidon Se7en rebreather, (Poseidon Diving Systems AB, Göteborg, Sweden), and the sodalime scrubber removing carbon dioxide (CO_2) was a SofnoDive 797 (Molecular Products Inc, Boulder, CO, USA).

Procedures

Prior to each experiment, the subject underwent a medical check-up to ensure that he was "fit to fly." Thereafter, the subject, who was dressed in shorts and gym shoes, performed 150 knee squats in 10 min to create a normalized baseline for venous bubble micronuclei.[9] The subject was instrumented with pre-gelled electrodes for electro- (ECG) and impedance cardiography. He was then positioned on his left side in a horizontal recumbent position on a gurney inside the hypobaric chamber.

A four-chamber view of the heart was monitored for VGE and the presence of VGE was scored using the Eftedal-Brubakk 5-point scale (0 = no visible bubbles, 1 = occasional bubbles, 2 = at least one bubble every fourth heartbeat, 3 = at least one bubble every heartbeat, 4 = at least one bubble per centimeter squared).[18]

Heart rate (HR) was derived from ECG recordings with the electrodes in a precordial one-lead position. Cardiac stroke volume (SV) and output (CO) were determined and recorded beat-by-beat, with impedance electrodes placed at the base of the neck and on the thorax. The impedance calibration procedure recommended by the manufacturer was conducted before each experiment, while the subject was resting supine. S_pO_2 was monitored, with the sensor placed on the left index finger.

During each experiment, whole body washout and uptake of N_2 was assessed continuously using a system described in detail elsewhere.[23] Briefly, the subject was wearing a nose clip and breathing through a mouthpiece to and from a modified closed-circuit electronic rebreather. CO_2 was removed from the exhalation side of the system by means of a soda-lime scrubber, and oxygen (O_2) was injected automatically on the inhalation side to maintain O_2 partial pressure at a preset value (21 kPa). Thus, the rebreather system, which was used in combination with custom-made computer software, measures O_2 partial pressure, temperature and moisture in four different parts of the closed circuit. The elimination or uptake of N_2 was calculated by measurement of total gas volume in the closed rebreather system, subtracting the calculated volumes of water vapor and O_2.

Each subject was investigated in three different conditions:

- One 90-min continuous exposure to a simulated altitude of 24,000 ft (High);
- Three 30-min exposures to a simulated altitude of 24,000 ft interspersed by two 30-min intervals at 15,000 ft (High-Low); and
- One 90-min continuous exposure to a simulated altitude of 15,000 ft (Low).

The three trials were conducted in alternate order and, for the individual subject, separated by ≥ 72 h. The target rate of

ascent and descent was 5000 ft/min. The subject was breathing ambient (chamber) air at all simulated altitudes below 10,000 ft, during the initial ascent as well as the final descent (from and to ground level). To maintain normal oxygen saturation at altitudes above 10,000 ft, the subject was, during altitude transitions between 10,000 and 24,000 ft, breathing a premixed gas containing 46.5% O_2 and 53.5% N_2, via an oro-nasal mask provided with a constant flow from a bottle of compressed gas. Once the predetermined altitude (24,000 ft or 15,000 ft) was reached after the initial ascent, the subject exhaled to functional residual capacity (FRC), and was then connected to the rebreather, which was prefilled with 3.0 L of normoxic breathing gas (fractions of O_2: 53.3% at 24,000 ft and 36.7% at 15,000 ft; balance N_2). In all trials, a similar procedure, with exhalation to FRC, was used in instances when N_2 washout/uptake made it necessary to adjust the bellows volume. During the High-Low trial, the aforementioned rebreathing procedure was iterated during each 30-min period at 24,000 ft and 15,000 ft, respectively, and during the ascents and descents between 15,000 ft and 24,000 ft, the subject breathed the premixed gas (46.5% O_2), via an oro-nasal mask as described above.

VGE was assessed every 5 min, and in connection with this, the subject was asked for any symptoms and checked for signs of DCS. Every 15 min throughout each trial, the subject performed three unloaded knee bends while in the left-side horizontal recumbent position and assessment of VGE prevalence was made following the last knee bend. During the initial ascent from and final descent to sea level, a 1-min stop was made every 5000 ft for VGE examination. Responses for HR, SV, CO, S_pO_2 and N_2 balance were measured/estimated continuously throughout each experiment.

During each altitude exposure, the subject was accompanied by an inside experimenter (medical doctor), who performed the VGE and DCS assessments. End-point criteria for the altitude exposures were a consistent VGE score of 4 and/or symptoms/signs of DCS. The inside experimenter was breathing 100% O_2 via a full-face mask and a demand valve during, and for 1 h preceding each experiment. All experiments were surveilled continuously via a closed-circuit video/audio system (JVC MI-5000 Victor company, Tokyo, Japan) by a medical doctor and an experimenter, both positioned outside the chamber.

Statistical Analyses

To analyze the VGE data, which are ordinal data, a statistical procedure proposed by Baguley et al. was used.[1] The VGE data for all three series were rank transformed and the ranks were tested using a one-way repeated measures ANOVA; when the ANOVA indicated a significant difference, post hoc tests were carried out using Tukey HSD test. The N_2 exchange rate was calculated for each 30-min period and a one-factor repeated measures ANOVA was computed for each condition. For the HR and CO data, a repeated measures ANOVA was utilized. $P < 0.05$ was considered significant for all tested variables.

RESULTS

In all three conditions, the rates of ascent and descent were maintained at stipulated values, and in all experiments, chamber pressure was reached within 30 s from the targeted time. At altitude, each subject was connected to the rebreather and the data collection started in less than 150 s (mean 69 s, range 35–150 s). All subjects completed all three exposures. There was no incidence of DCS. All subjects exhibited S_pO_2 values above 95% throughout all exposures.

During condition High, VGE were observed in the right ventricle in all subjects within 45 min. In condition High-Low, right ventricle VGE were observed within 30 min at 24,000 ft in all but one subject, who did not exhibit any VGE during the entire experiment. The intra- and interindividual variability in decompression VGE in conjunction with diving has been described recently.[19] In condition Low, VGE were observed in only three subjects, of which two had a maximum score of 1 and one a maximum score of 2; these VGE seemingly appeared at random times during the 90 min at 15,000 ft. Five out of eight thus exhibited no VGE during condition Low (**Fig. 1A**). In condition High, there was a continuous increase in VGE scores with time both during rest and in conjunction with the knee bends (**Fig. 1B**).

In condition High-Low (**Fig. 1C**), most subjects exhibited only low VGE scores during the first period at 24,000 and 15,000 ft, respectively. However, the majority of the subjects showed a gradual increase in VGE scores during the following periods at 24,000 ft.

In the High-Low condition, the excursions between 24,000 and 15,000 ft demonstrated significant changes in the VGE scores [$F(4,28) = 8.3$; $P < 0.001$]. The excursions to 15,000 ft reduced the knee-bend VGE scores, with lower values during the first period at 15,000 ft than the first period at 24,000 ft ($P < 0.01$), and lower than during the second period at 24,000 ft ($P < 0.01$). Likewise, knee-bend VGE scores were lower during the second exposure at 15,000 ft than the third exposure at 24,000 ft ($P < 0.01$). At rest, the VGE scores [$F(4,28) = 7.36$, $P < 0.001$)] were lower during the first 15,000 ft exposure than during both the first 24,000 ft exposure ($P < 0.05$) and the second 24,000 ft exposure ($P < 0.05$). Likewise, resting VGE were lower during the second 15,000 ft exposure than during both the second ($P < 0.05$) and the third exposure at 24,000 ft ($P < 0.01$) (Fig. 1C).

Comparing the median peak VGE scores did not reveal any statistically significant difference between conditions High and High-Low, neither at rest [High, median: 1, range (0–3); High-Low, median: 2, range (0–3)] nor during knee-bends [High, median: 3, range (1–4); High-Low, median: 3, range (0–4)]. However, both High and High-Low induced more bubbles than did Low [Low rest, median: 0, range (0–1); Low knee-bends, median: 0, range (0–2)] both at rest [$F(2.14) = 24.94$, $P < 0.001$, post hoc $P < 0.01$] and in conjunction with the knee-bends [$F(2.14) = 16.76$, $P < 0.001$, post hoc $P < 0.01$] (Fig. 1A and Fig. 1B).

During the initial ascent from sea level to altitude, no VGE were noted in any of the three conditions (**Table I**). During

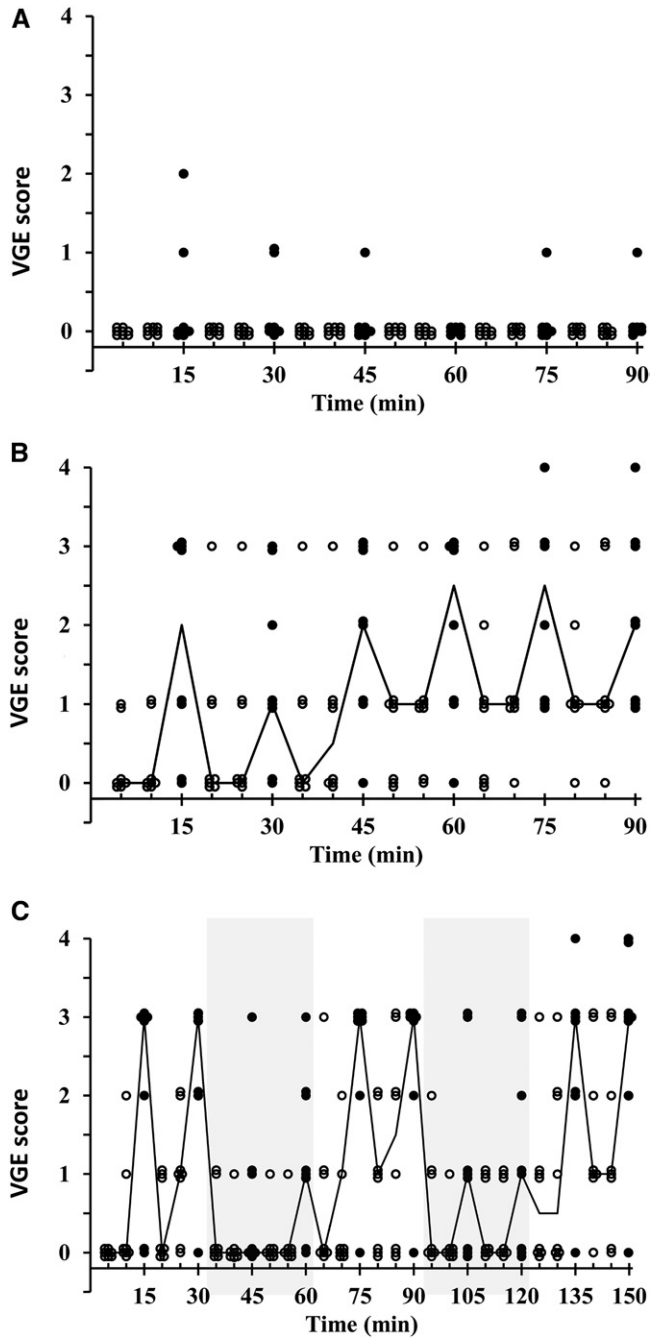

Fig. 1. Venous gas emboli (VGE) scores during conditions: A) Low (15,000 ft); B) High (24,000 ft); and C) High-Low (24,000 vs. 15,000 ft). Filled symbols denote values in conjunction with knee bends and open symbols values during rest. Continuous lines denote median values; $N = 8$.

descent from 24,000 ft in condition High, resting VGE dropped substantially [$F(4,28) = 14.33$; $P < 0.001$] with a significant reduction after reaching 10,000 ft ($P < 0.01$). Likewise, during descent in condition High, a drop in VGE scores in conjunction with the knee-bends was noted [$F(4,28) = 11.48$, $P < 0.001$] once 15,000 ft had been reached ($P < 0.05$), with further reductions at 10,000 ft, 5000 ft, and sea level ($P < 0.01$; **Table II**). However, one subject with a BMI of 32.7 kg · m^{-2} (mean for all subjects was 28.7 kg · m^{-2}) continued to produce profuse amounts of bubbles until sea level had been reached. This subject also had a high N_2 washout during the last 30 min at 24,000 ft (7.9 ml · min^{-1}, mean for all subjects was 4.84 ml · min^{-1}).

During descent from 24,000 ft in condition High-Low, no change in VGE scores was seen until an altitude of 5000 ft had been reached either at rest or during knee-bends [$F(4,28) = 7.44$, $P < 0.001$], with a significant change in bubble scores from 24,000 ft to 5000 ft ($P < 0.01$) and sea level ($P < 0.01$; Table II), or at rest [$F(4,28) = 10.2$, $P < 0.001$; $P < 0.01$ at 5000 ft and $P < 0.001$ at sea level; Table I]. Three of the seven subjects still showed some bubbles after reaching sea level. No VGE were seen during descent from condition Low in any of the subjects.

A gradual exponential decrease in N_2 elimination rate was observed over time in condition High and condition Low. The average elimination rate (ER) fell according to the equation ER = (14.8 ± 9.31) exp((−0.015 ± 0.006)×t) at 24,000 ft, and ER = 5.9 ± 2.49 exp((−0.016 ± 0.008)×t)) at 15,000 ft, where t = time in minutes. This gives a whole-body half-time for N_2 washout of roughly 45 min. In condition High-Low, a substantial N_2 uptake was noted during the second excursion to 15,000 ft ($P = 0.025$; **Fig. 2**).

In the first 30 min in condition High (12.0 ± 6.0 ml · min^{-1}) the washout rate was similar to the washout rate during the initial period at 24,000 ft in condition High-Low (11.8 ± 4.7 ml · min^{-1}). The washout rate during the first 30 min during condition Low (4.7 ± 1.5 ml · min^{-1}) was significantly lower than in condition High and High-Low [$F(2,14) = 8.61$, $P < 0.001$].

HR decreased slowly over time in all conditions from 80 ± 14 beats per minute (bpm) to 67 ± 8 bpm in High ($P = 0.002$), from 79 ± 8 bpm to 62 ± 7 bpm in High-Low ($P < 0.001$), and from 75 ± 9 bpm to 64 ± 8 bpm in Low ($P = 0.015$). Likewise, CO slowly decreased over time from 9.0 ± 1.6 L · min^{-1} to 6.4 ± 1.5 L · min^{-1} in High ($P = 0.002$), and tended to decrease during the course of the Low condition from 10.3 ± 3.6 L · min^{-1} to 7.5 ± 2.5 L · min^{-1} ($P = 0.095$), but with no change in High-Low (8.7 ± 2.2 L · min^{-1} at the start and 6.1 ± 2.6 L · min^{-1} at the end of the test; $P = 0.12$).

DISCUSSION

The aim was to compare DCS risk during sustained vis-a-vis intermittent exposure to simulated high altitude. The results showed that during the 90-min continuous exposure to 24,000 ft (High), the occurrence of VGE was substantial and appeared to increase with exposure time, whereas identical exposure duration at 15,000 ft (Low) induced but sporadic VGE. The excursions from 24,000 to 15,000 ft (High-Low) temporarily reduced, but did not abolish, the VGE scores so that at any given cumulated time at 24,000 ft, the prevalence of VGE was similar in the High and High-Low conditions. Moreover, during the final step-wise descent from 24,000 ft, VGE appeared more persistent after the High-Low than after the High exposure. In both High and Low, whole-body N_2 was washed out at

Table I. VGE Scores During Rest for Conditions High, High-Low, and Low During the Transition from Ground to 24,000 ft (High and High-Low) or to 15,000 ft (Low) and Back to Ground Level at the End of the Test.

	ASCENT (FEET)					DESCENT (FEET)					
CONDITION	**5000**	**10,000**	**15,000**	**20,000**	**24,000**	**24,000**	**20,000**	**15,000**	**10,000**	**5000**	**GROUND**
High	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	1 (0–3)	1(0–3)	0 (0–3)	0 (0–3)**	0 (0–3)**	0 (0–3)**
High-Low	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	1 (0–3)	2(0–3)	1 (0–2)	1 (0–2)	0 (0–1)***	0 (0–1)***
Low	0 (0–0)	0 (0–0)	0 (0–0)					0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)

Data are median (min-max); $N = 8$. Difference cf. 24,000 ft (for High and High-Low): $^{**}P < 0.01$; $^{***}P < 0.001$.

an exponentially decaying rate, whereas in High-Low, the N_2 washout at 24,000 ft was interrupted during the first excursion to 15,000 ft and a significant N_2 uptake occurred during the second excursion to 15,000 ft.

As noted above, the high and increasing prevalence of VGE at high altitude in the High condition confirms previous results,[6,21,32] and suggests that prolonged normoxic exposure to 24,000 ft is associated with a substantial risk of developing DCS, given that high scores of VGE, as determined from audio Doppler or ultrasound imaging techniques of the right heart, appear to be valid predictors of DCS risk[3] both during altitude exposures and after diving,[5,11,15] although VGE scores are generally a better negative than positive predictor of DCS.[16,18] The low prevalence of VGE during Low is also in good agreement with previous studies,[29,30] and suggests that the decompression stress induced by a step-change in altitude from sea level to 15,000 ft is sufficiently mild to only induce evolution of very few gas bubbles in blood or other tissues.

It thus appears reasonable to assume that the excursions to 15,000 ft in the present High-Low experiments did not contribute to VGE formation. This does not exclude that periods at this altitude might have contributed to growth of already existing gas bubbles during subsequent high altitude periods, by increasing PN_2 and hence reloading of the N_2 stores in the body. The observed stop in pulmonary wash-out of N_2 during the first excursion to 15,000 ft and a significant uptake during the second one supports the notion of concomitant maintenance or partial replenishment of body N_2 stores. That the excursion-induced N_2 uptake resulted in renewed supersaturation of N_2 during the subsequent periods at 24,000 ft is supported by the finding that the overall net N_2 elimination rate was considerably slower in High-Low than in High (3.8 ± 2.7 ml $\cdot$ min^{-1} vs. 7.2 ± 3.4 ml $\cdot$ min^{-1}, $P < 0.01$). The relatively high PN_2 during the second and third periods at 24,000 in High-Low may thus have facilitated N_2 diffusion into the VGE and hence might have served to increase final gas-bubble size in High-Low compared to in High.

According to the Young-LaPlace equation ($\Delta P = 2\ \gamma/r$), where γ is the surface tension, the excess pressure (ΔP) inside a gas bubble immersed in a liquid is inversely proportional to its radius (r). The larger the bubble the less is the excess gas pressure inside the bubble, and the less is the outward diffusion rate of the gas. Thus, an increase in ambient pressure will cause bubbles to decrease in volume by two mechanisms, the Boyle compression and an increased outward diffusion rate of gas. Consequently, the fact that the VGE were more persistent during the final descent in High-Low than in High might reflect larger bubble size during the former condition. It is also possible that time-dependent accumulation in the VGE surface film of hydrophobic proteins or other surface-tension reducing molecules[14,25] may have contributed to a lowering of the surface tension and an increased compression resistance of VGE during the High-Low descent. Gradually increasing VGE size may also partly explain the observed altitude-VGE score hysteresis between ascent and descent, with higher scores at any given altitude during descent than ascent.

It is noted that the reduction in a spherical bubble radius during compression from 24,000 ft (≈40 kPa) to 15,000 ft (≈58 kPa) will be less than 15%. However, it can be calculated using the Epstein-Plesset equation that due to the outward diffusion of nitrogen, gas bubbles of radii larger than 100 μm will be reduced in size below the detection limit of the present ultrasound technique, which is a diameter of 20–30 μm,[7,18] between consecutive ultrasound measurements after such a compression.[10,19] Thus, there is a relatively wide range of bubble sizes that theoretically would disappear from view after a compression from 24,000 to 15,000 ft.

Upon a rapid ascent to high altitude, the washout rate of N_2 from a given tissue compartment is largely determined by the combination of its blood perfusion rate and its N_2 solubility, with tissues being categorized as fast, intermediate or slow responding.[2,13,17] DCS at altitude commonly develop with a considerable latency from the time of ascent to high altitude, and release of N_2 from slow tissue compartments have been

Table II. VGE Scores After Knee Bends for Conditions High, High-Low, and Low During Transition from Ground to 24,000 ft (in High and High-Low) or 15,000 ft (in Low) and Back to Ground Level.

	ASCENT (FEET)					DESCENT (FEET)					
CONDITION	**5000**	**10,000**	**15,000**	**20,000**	**24,000**	**24,000**	**20,000**	**15,000**	**10,000**	**5000**	**GROUND**
High	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	2 (1–4)	1(0–4)	0 (0–4)*	0 (0–4)**	0 (0–3)**	0 (0–3)**
High-Low	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	3 (2–4)	3(2–3)	3 (1–3)	3 (0–3)	1 (0–3)**	0 (0–3)**
Low	0 (0–0)	0 (0–0)	0 (0–0)					0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)

Data are median (min-max); $N = 8$. Difference cf. 24,000 ft (for High and High-Low): $^{*}P < 0.05$; $^{**}P < 0.01$.

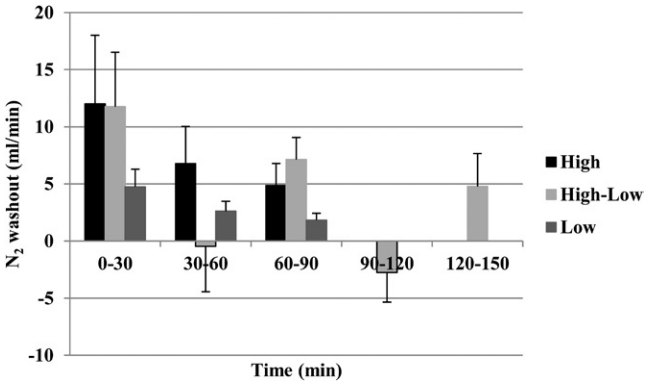

Fig. 2. Nitrogen (N_2) washout and uptake (ml · min^{-1}) in conditions High, High-Low, and Low. Values are mean and SD; $N = 8$.

attributed a dominant role in the development of DCS.[4,27] Although N_2 release from slow and intermediate tissues must have contributed to the gradual increase in VGE occurrence in the present High condition, several findings seem to suggest that the VGE were predominantly formed early following ascent and then sustained throughout the remaining high-altitude exposure. Thus, in the High condition, the rapid drop in whole-body N_2 elimination rate following decompression would reflect a concomitant drop in the supersaturation level of N_2 in mixed venous blood. Therefore, and because VGE were observed already after 15 min at 24,000 ft in the High and High-Low trials, it appears that in these conditions formation of VGE was an early event upon ascent. As noted above, the present ultrasound technique is not capable of detecting VGE smaller than about 20–30 μm and hence it appears likely that micro VGE had developed already before 15 min at 24,000 ft in the High and High-Low conditions. The observations that following each excursion down to 15,000 ft in the High-Low condition, the VGE scores returned to pre-excursion within the first or second measurement after the subjects were returned to 24,000 ft, as well as the aforementioned finding that the compressibility of the VGE upon descent from 24,000 ft appeared to be inversely related to the duration of the high-altitude exposure, suggest that, once formed, the VGE were rather persistent. Theoretical models and in vitro studies suggest that the critical radius for stable gas bubbles in liquid environments is 2–4 μm.[26,31] In vivo studies, employing a dual-frequency ultrasound technique, have shown that gas bubbles of < 10 μm may persist in the blood stream of swine exposed to severe decompression stress.[23]

Our finding that the excursions from 24,000 to 15,000 ft did not eliminate the VGE should be viewed in the context of a previous study demonstrating that 20-min excursions to 900 ft abolished VGE formed at 24,000 ft.[32] It appears that during high-altitude exposure interrupted by intermittent excursions to lower altitude, the elimination of VGE is predominantly determined by the magnitude of the pressure increase, whereas the duration of the excursions to low altitude plays a minor role. Thus, Pilmanis and coworkers[21] showed that excursions from 25,000 ft to sea level reduced the incidence of DCS and VGE to similar extent whether the low-altitude excursions were maintained for an hour or only for a very brief moment. However, one should note that in that study, whereas the amount of VGE during the interrupted altitude exposures was significantly lower than for the continuous exposure for a similar cumulative time at high altitude, there was still an increase in VGE incidence with time,[21] even for the interrupted exposures. That would indicate that the bubbles had not completely disappeared even after 1 h at ground level. Similarly, in our previous study after three 20 min exposures to 24,000 ft and three 20 min sojourns to 900 ft, bubbles started to appear during the fourth and last 20 min exposure to 24,000 ft.[32] Thus, it would appear that both pressure and time at lower altitude is of importance for removing the bubbles. It can also be speculated that there may be an optimal time at a given lower altitude depending on the time to remove all gas from the bubbles in comparison to the time of on-gassing N_2 in the tissues.

The operational problem most relevant to the present study is, as mentioned, long-duration high-altitude flying in fighter aircraft. Current Swedish regulations stipulate that, at cabin altitudes above 22,000 ft, continuous flying time should not exceed 30 min, but no guidelines are given regarding safe magnitude and duration of the intermittent excursions to lower altitude. Our choice of 15,000 ft cabin altitude during the excursions was dictated by the fact that this constitutes a low but realistic cabin altitude for in-air refueling, as well as by our previous finding that excursions to 20,000 ft will, if anything, increase the risk of DCS.[32] Present results clearly show that under normoxic conditions, alternating the cabin altitude between 24,000 and 15,000 ft during long-duration flight is not safe from a DCS perspective. Possibly, excursions to even lower cabin altitudes might alleviate the risk of altitude DCS, although this would likely exclude in-air refueling from a strategic tanker. Moreover, in an operational setting, the pilot would breathe hyperoxic rather than normoxic gas mixtures. It is well established that breathing hyperoxic gas mixtures reduces the risk of developing DCS.[28] Whether per- and/or preoxygenation regimens might prevent or substantially reduce the development of VGE during sustained and intermittent high-altitude exposures, such as the present, remains to be settled.

Other operational situations that may require repeated exposures to low ambient pressure include military high-altitude parachuting/skydiving from aircraft with unpressurized cabins, where particularly the loadmaster and the jumpmaster may be exposed to a sequence of episodes at high altitude.

In conclusion, present results suggest that, during normoxic conditions, long-duration flying at a cabin altitude of 24,000 ft is associated with substantial production of VGE, and presence of bubbles is not reduced by intermittent excursions to a cabin altitude of 15,000 ft apart from the actual period at the higher pressure. By contrast, the reduced compressibility of VGE during descent from 24,000 ft in the High-Low condition suggests that such excursions to 15,000 ft might even increase the DCS risk.

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