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HIGHLIGHTED TOPIC | *The Physiology and Pathophysiology of the Hyperbaric and Diving Environments*

Decompression to altitude: assumptions, experimental evidence, and future directions

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Foster PP, Butler BD. Decompression to altitude: assumptions, experimental evidence, and future directions. *J Appl Physiol* 106: 678–690, 2009. First published December 12, 2008; doi:10.1152/japplphysiol.91099.2008.—Although differences exist, hypobaric and hyperbaric exposures share common physiological, biochemical, and clinical features, and their comparison may provide further insight into the mechanisms of decompression stress. Although altitude decompression illness (DCI) has been experienced by high-altitude Air Force pilots and is common in ground-based experiments simulating decompression profiles of extravehicular activities (EVAs) or astronauts' space walks, no case has been reported during actual EVAs in the non-weight-bearing microgravity environment of orbital space missions. We are uncertain whether gravity influences decompression outcomes via nitrogen tissue washout or via alterations related to skeletal muscle activity. However, robust experimental evidence demonstrated the role of skeletal muscle exercise, activities, and/or movement in bubble formation and DCI occurrence. Dualism of effects of exercise, positive or negative, on bubble formation and DCI is a striking feature in hypobaric exposure. Therefore, the discussion and the structure of this review are centered on those highlighted unresolved topics about the relationship between muscle activity, decompression, and microgravity. This article also provides, in the context of altitude decompression, an overview of the role of denitrogenation, metabolic gases, gas micronuclei, stabilization of bubbles, biochemical pathways activated by bubbles, nitric oxide, oxygen, anthropometric or physiological variables, Doppler-detectable bubbles, and potential arterialization of bubbles. These findings and uncertainties will produce further physiological challenges to solve in order to line up for the programmed human return to the Moon, the preparation for human exploration of Mars, and the EVAs implementation in a non-zero gravity environment.

bubble; decompression illness; exercise; microgravity

AS PART of the Highlighted Topics series entitled "The Physiology and Pathophysiology of the Hyperbaric and Diving Environments," this minireview outlines the role of oxygen prebreathe, micronuclei of gases, metabolic gases, nitric oxide, exercise, and gravity in the physiology of gas bubbles and in the potential occurrence of decompression illness (DCI) symptoms while breathing gases at a pressure lower than ambient atmospheric pressure at sea level. Although differences exist, hypobaric and hyperbaric exposures share common physiological, biochemical, and clinical features. The primary differences are in the onset of symptoms. In hypobaric decompression, the onset of symptoms is most likely to occur while aviators or astronauts are still engaged in the excursion at a reduced atmospheric pressure; therefore, if DCI occurs, the completion of the mission will be affected. On the other hand, in hyperbaric decompression, the onset of symptoms generally occurs after the pressure excursion, and deep sea divers, for instance, are typically at risk of developing DCI only on return to the surface at the conclusion of the dive.

Robert Boyle (20), in 1670, reported the first observation of rapid occurrence of numerous gas bubbles in animals subjected to reduced atmospheric pressures in his newly invented air pump. He mentioned the obstruction of vessels by small bubbles and the pain produced by bubbles distending tissues. When hot air balloons were capable of reaching high altitude with a rapid ascent by other means than slower mountain climbing, humans started to experience symptoms resembling those of caisson disease or those of undersea divers (55). The association of hypobaric decompression to specific symptoms was reported by Paul Bert (17) with his citation of Glaisher and Coxwell's experience following a rapid ascent (305 m/min) to

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29,000 ft (8,838 m) in their balloon in 1862. He described a paralysis of the left arm spontaneously resolving on recompression while returning to the ground (17).

PERSPECTIVE AND RATIONALE FOR HYPOBARIC DECOMPRESSION

In more current applications, hypobaric decompression and the associated DCI are reported in high-altitude aviators and astronauts (40, 58, 104). The human return to the Moon, and preparation for human exploration of Mars, long-duration (six mo) missions on lunar or Mars outposts (6–30 mo), will require numerous space walks or extravehicular activities (EVAs) within a space suit during orbital flights or on the surface. Astronauts performing EVAs are subjected to a reduced absolute pressure of approximately one-third the standard atmospheric pressure, 30 kPa [fraction of inspired O_2 ($F_{I_{O_2}}$) = 1], within the space suit (35, 36, 38, 129). The rationale for having such a mildly pressurized suit is to minimize the pressure gradient across the suit to provide an enhanced mobility and dexterity. Those EVAs will be required for assembling structures or exploring and will be critical in providing skeletal muscle exercise as a countermeasure during long-duration missions to cardiovascular deconditioning, confinement, muscle atrophy, and bone loss. Besides decompressions encountered in the Space Program, critical hypobaric decompressions may also be experienced in civilian or military aircraft (104, 106). In the Air Force U2 reconnaissance aircraft, the risk of DCI has even been estimated as high as 75% (104). Clearly, in response to a reduction of the absolute ambient pressure of the breathing medium, symptoms of DCI may occur (9, 33, 40, 58, 105, 106). Indeed, the primary cause of DCI is the de novo gas bubble formation and their growth within tissues evolving from dissolved gases (34, 35, 38, 58). Over the past decades, great strides have been made in the understanding of hypobaric physiology. Prevention of hypobaric or altitude DCI has involved oxygen prebreathing (before and during hypobaric exposure), staged decompression, and other modalities, although full protection against DCI has yet to be achieved. The aims of this review are *1*) to summarize the well-established biology of bubble formation; *2*) to analyze the evidence that certain physiological procedures such as oxygen prebreathe including specific skeletal muscle exercises, may prevent the occurrence of DCI; and *3*) to outline unresolved questions.

BUBBLE FORMATION AND GROWTH: RESEMBLANCE AND DIFFERENCE WITH HYPERBARIC DECOMPRESSION

Supersaturation, gas micronuclei, and explosive bubble growth. During a reduction of both the absolute ambient pressure of the breathing medium and the inspired partial pressure of nitrogen (N_2), $P_{I_{N_2}}$, along with the absence of a significant increase in inspired partial pressure of oxygen (O_2), $P_{I_{O_2}}$, bona fide bubbles may be generated in tissues supersaturated with N_2 from primordial small ($\approx$1–3 μm in diameter) gaseous entities, "gas micronuclei" (51, 58, 66, 116, 118, 122). The initial explosive bubble growth involves the surrounding tissue (118) and may recruit all available gases, including metabolic gases, carbon dioxide (CO_2), O_2, and water vapor (57, 117). The importance of the mechanistic role of metabolic gases in bubble formation seems to be related to their significant driving pressure during hypobaric decompression, estimated to be approximately the sum of their mixed venous blood (or tissue) tensions (57). Oxygen breathing at the barometric pressure (total pressure of gases in the breathing medium; P_B) of 71 kPa ($F_{I_{O_2}}$ = 1) induced further bubble growth in rats previously exposed to only relatively mild hypobaric decompressions (P_B = 71 kPa, $F_{I_{O_2}}$ = 0.2094) (72). In hyperbaric decompressions, contribution of metabolic gases as a significant fraction of internal gases constituting bubbles has also been reported (131) or as participating in the bubble growth (71). The crucial process for generating a bona fide bubble is the overcoming of the surface tension pressure by the driving pressure of excess dissolved gas which is suddenly entering the bubble (22, 146, 149). This inward diffusion of gas into the bubble is enough to reach its critical radius from which the bubble will expand rather than shrink (149). If the overwhelming of surface tension is essential to bubble formation during decompression, a larger absolute pressure drop in the breathing medium is expected to give rise to a higher bubble density per unit volume of tissue (22, 118, 149). Therefore, considering a sea-level ambient atmosphere (P_{atm}) starting point, we can anticipate a lower density of bubbles in hypobaric decompression with approximately a three-time maximum drop of absolute inspired pressure within the EVA suit ($P_{1/3atm}$) compared with a higher density due to increases of absolute inspired pressure over four (P_{4atm}), five (P_{5atm}), or six times (P_{6atm}) the initial P_{atm} in diving. Furthermore, in hyperbaric decompressions the supersaturated tissue in inert gas becomes a long-lasting reservoir for N_2, whereas in hypobaric decompressions rapid and massive diffusion of N_2 into the bubble from neighboring tissue with limited N_2 stocks leads to the depletion of N_2 in the tissue and stops further bubble growth (22, 118).

Stabilization of hypobaric bubbles. Bubbles in tissues or intravascular bubbles can be stabilized by a coating layer and persist much longer than a simple uncoated gas bubble (123). The presence of bubbles in blood affects many cascading systems, such as *1*) adsorption of plasma proteins, phospholipids, and fibrinogen; *2*) activation of complement, Hageman, leukocytes, platelet, thrombin, and phospholipase; and *3*) lipid peroxidation (29, 85). Leukocytes and platelets have been demonstrated to adhere to bubbles (1, 99, 113). Neutrophil activation was reported with hyperbaric decompression (15). Attraction of neutrophils to the gas bubbles is triggered by a number of chemotactic factors (77). Although it is probable that surface-active molecules in blood or other tissues aggregate at bubble surfaces (85, 88), it is not well established that these layers have an effective stabilizing action (119). However, it has been suggested that structural stabilizers such as surfactant monolayers may perpetuate gas micronuclei or small gas bubbles (42, 148), precursors of larger bubbles that may cause damage to tissue. Observation of micronuclei coated by surfactant in distilled water and gelatin has been reported (147). When a bubble is stabilized by surfactant monolayer, likely lipid, permeability to gases would be high (119). Therefore, bubbles are permeable to inward and/or outward diffusion of gases according to the gas partial pressure gradients across the bubble wall. Simulations of diffusive gas exchanges across the bubble-tissue interface are rapid enough to bring the bubble to its stable radius (23, 121). However, in hypobaric decompressions, the low tissue N_2 supersaturation and the insufficient

reserves of dissolved gases in tissues will not indefinitely supply permeating gases for inward diffusion into the bubble to further stabilize the bubble (119). Therefore, in that case, surfactant is likely to play a major role in stabilizing persistent bubbles. The site of bubble nucleation and formation is probably extracellular, since N_2 supersaturation of ~30,000 kPa (300 atm) followed by rapid decompression is required for intracellular formation (67). This level of supersaturation is higher than the nucleation threshold for aqueous solutions (54, 68) and well above that of hypobaric decompressions, therefore ruling out the possibility of intracellular formation of bubbles during hypobaric decompressions (66, 69). Experimental evidence exists for preexisting gas micronuclei in animals before the beginning of any decompression (54, 66, 125). If this hypothesis is true, applying a high-pressure treatment, which provides a crushing pressure for gas micronuclei before decompression (116), would entail a postdecompression reduction of bubble formation (54) and DCI (125). Repetitive hyperbaric exposures constituted a predecompression treatment that might have provided a beneficial acclimatization to decompression stress in professional divers (54). Therefore, reduction of micronuclei density may also be relevant to prevent occurrence of bubbles and DCI during hypobaric decompression. Most of the preventive procedures have to take place before the hypobaric decompression such as with EVA since the decompression within the suit and the breathing of a low-pressure mixture is already part of the critical operational time.

OXYGEN PREBREATHE

During normal breathing conditions at 1 atm, N_2 in tissues of the human body is equilibrated with the N_2 alveolar partial pressure ($P_{A_{N_2}}$ = 76 kPa = 570 mmHg). To reduce bubble formation and growth during hypobaric exposures, a denitrogenation or N_2 "washout" procedure consists of prebreathing a mixture with a low N_2 partial pressure usually enriched with O_2 ($P_{I_{O_2}} > 21.3$ kPa = 160 mmHg), before the ascent to the working altitude or space suit pressures (33, 35, 36, 38, 58, 101, 105, 122, 137). For example, breathing the following medium, $F_{I_{O_2}} = 1$ at $P_B = P_{I_{O_2}} = 101.3$ kPa (760 mmHg) with $P_{I_{N_2}} = 0$, has been extensively used (35–37) and provides an efficient denitrogenation at sea level before hypobaric decompression. Such a considerable N_2 pressure gradient from tissues to alveoli eliminates excess dissolved N_2 from tissues into the expired air. A disconcerting question about O_2 prebreathe is how such a considerable N_2 tissue supersaturation does not produce bubbles or DCI. Is the $P_{I_{N_2}}$ reduction during O_2 prebreathe sufficient for safe tissue off-gassing in the "prebend" altitude zone? Does a high $P_{I_{O_2}}$ preclude preexisting micronuclei or prevent bubble formation and growth from micronuclei?

OXYGEN PREBREATHE AND GAS MICRONUCLEI

A role for oxygen? A possible role for high P_{O_2} in the depletion of the internal gas within micronuclei has been suggested from an experiment in crustaceans (5). Gases occupying the micronucleus may be exchanged with a gas in the surrounding tissue such as O_2 by simple diffusion. The counterdiffusion has been initially described for inert gases (41, 65), which follow a combination of Fick's first phenomenological law of diffusion (65). However, the reciprocal exchange of O_2 and N_2, N_2 diffusing out of the bubble in exchange of O_2 diffusing in (5), should be considered, since molar fluxes of permeating ideal gas species, both inert and metabolic, obey Fick's first phenomenological law of diffusion across the boundary layer coating the bubble (59). Oxygen might later diffuse out of the gas micronuclei or the newly forming bubble to be utilized in tissue metabolism. Eventually, micronuclei are eliminated and bubble formation is reduced during decompression (5). Increasing P_{O_2} above 101.3 kPa (P_{O_2} = 405 kPa) before decompression brought about in crustaceans a reduction of density and total volume of bubbles (53). Butler at al. (30) showed that hyperbaric hyperoxia ($P_B = P_{I_{O_2}} = 285.1$ kPa) reduced the incidence, severity, and complications of DCI in a higher species such as rat. However, prolonged breathing of hyperoxic mixtures in humans may expose them to a risk of oxygen toxicity and may induce a shift of the cardiovascular and respiratory response against the respiratory elimination of N_2. Compared with normobaric normoxic condition, hyperbaric hyperoxic mixtures deter the respiratory elimination of N_2 whereas normobaric hypoxic mixtures ($P_{I_{O_2}}$ = 11.5 kPa = 86 mmHg) enhance N_2 washout (4). Therefore, the overall positive effect of oxygen, leading to a potential reduction of both bubble growth and micronuclei density, may be mitigated or even overwhelmed by the cardiorespiratory effects of hyperoxia. Clearly, hypoxia induces increases in heart rate, cardiac output, ventilation, and skin and skeletal muscle blood flow, which facilitate N_2 washout (4, 76), while hyperoxia causes opposite effects (4).

Interruption of oxygen prebreathe. Oxygen prebreathing for several hours is required to eliminate the excess dissolved N_2 from slow tissues that can potentially generate damaging hypobaric decompression bubbles. Because of operational time constraints, potential fire hazards (3), and oxygen toxicity with high $F_{I_{O_2}}$ during space missions, the optimal case for inspired O_2 fraction and pressure cannot be achieved and thus in most cases $P_{I_{N_2}} \neq 0$. Nonzero $P_{I_{N_2}}$ are frequently included in the breathing medium, such as for specific prebreathe procedures utilized in the Space Program. However, these procedures are a tradeoff since it is widely agreed that the level of respiratory N_2 elimination is inversely proportional to $P_{I_{N_2}}$ in the breathing gas. To illustrate the effect of nonzero $P_{I_{N_2}}$, the following prebreathe mixtures before decompression to 30 kPa [$F_{I_{O_2}} = 1$, fraction of inspired N_2 ($F_{I_{N_2}}$) ≤ 0.004] have been tested (12): *1*) two-hour prebreathe with $F_{I_{O_2}} = 0.9–0.86$, $F_{I_{N_2}} = 0.1–0.14$, at ambient sea-level atmospheric pressure; and *2*) 2-h prebreathe with $F_{I_{O_2}} = 0.99–0.95$, $F_{I_{N_2}} = 0.004–0.05$, including a 3- to 10-min interruption breathing air ($F_{I_{O_2}} = 0.21$, $F_{I_{N_2}} = 0.79$), at ambient sea-level atmospheric pressure. The results demonstrated that $F_{I_{N_2}} \geq 0.1$ or a short interruption with air breathing produced a significantly higher incidence of DCI than an uninterrupted 2-h prebreathe with $F_{I_{O_2}} = 0.996–0.95$, $F_{I_{N_2}} = 0.004–0.05$ and thus neutralized the positive effects of O_2 prebreathe albeit $F_{I_{O_2}}$ was in the range of 0.86–0.99. This suggests a probable lack of complete N_2 desaturation of critical tissues in *case 1* and a N_2 resaturation of some critical tissues in *case 2*. It has long been known that an increased duration of preoxygenation delays the occurrence of symptoms (13). Indeed, an inverse correlation of incidence of symptoms and presence of Doppler-detected bubbles in the pulmonary artery to the length of O_2 prebreathing time has been found (129). Duration of O_2 prebreathe (P_B = 101.3 kPa, $F_{I_{O_2}} = 1$) before altitude exposure (P_B = 30 kPa, $F_{I_{O_2}} = 1$) ranged from 3.5 to

8 h; 8 h produced a complete disappearance of bubbles and symptoms of DCI (129). Increasing the suit pressure, and thus breathing a higher $P_{I_{O_2}}$, reduces the requirement for prebreathing, so that at higher $P_{I_{O_2}}$shorter or even no prebreathing is deemed necessary (129).

THRESHOLD ALTITUDE

In the absence of preoxygenation, a threshold altitude was found (138) to be *1*) ~4,500 m (P_B = 57 kPa, $F_{I_{O_2}}$ = 1) for first appearance of Doppler-detectable bubbles; and *2*) approximately 5,800–6,500 m (P_B = 48–44 kPa, $F_{I_{O_2}}$ = 1) for 5% DCI incidence with 95% confidence limits interval. The rate of ascent was 1,525 m/min and $F_{I_{O_2}}$ = 1, both during the ascent and the sojourn at altitude. At ~6,462 m (P_B = 44.1 kPa, $F_{I_{O_2}}$ = 1), venous gas emboli (VGE) incidence was ~50%. The DCI incidence in this experiment was ~50% at 7,000 m (P_B = 40 kPa, $F_{I_{O_2}}$ = 1) and climbed abruptly thereafter to 90% and up at 7,620 m (P_B = 38 kPa, $F_{I_{O_2}}$ = 1). Without preoxygenation, incidence of neurological, respiratory, and other serious symptoms increased with altitude from 0% at 6,462 m to 24% at 7,620 m (138). The threshold altitude without preoxygenation is higher if low $F_{I_{N_2}}$ and high $F_{I_{O_2}}$ are breathed at altitude, rate of ascent is lowered, or the length of stay at altitude is shortened (8, 105, 135, 138).

ANTHROPOMETRIC AND PHYSIOLOGICAL VARIABLES AFFECTING N_2 WASHOUT

Relevant variables. The threshold altitude may also be affected by individual variations such as *1*) augmented susceptibility to bubble formation with increase in age (39) and height (39); *2*) higher incidence of DCI with increase in age (112) and lower maximal aerobic capacity (136); and *3*) increase in height, weight, body mass index (BMI), body fat, and hormonal contraception that produced a higher DCI incidence when comparing high- to low-end values (134). Sex difference, per se, did not seem to affect bubble formation or DCI (39, 134).

Potential physiological mechanisms associated with these variables. Indeed, there is a decline of lung volumes and flows with age; age induces a decrease in forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1), FEV_1/FVC, and forced expiratory flows (45), whereas the residual volume is increased. Aging is also associated with left ventricular and arterial stiffening, an impairment of the ventricular-arterial coupling of the dynamic Starling mechanism (111), and a decrease of maximum cardiac output. These cardiovascular and respiratory alterations with aging probably lead to a less efficient respiratory elimination of N_2 from tissues in older subjects. Although the existence of a relationship between anthropometric variables and DCI was found, the insufficient goodness of fit did not allow the design of a predictive DCI model based on those independent variables (136). The higher incidence of bubbles and DCI with increases in height, weight, and BMI is related to an increased initial N_2 content in the whole body so that extended O_2 prebreathe time is required to eliminate N_2 from tissues. The initial N_2 content in the whole body is sometimes calculated (12). The total amount of an inert gas available from a tissue is set by its solubility within this tissue (120). Because solubility of all gases including N_2 is greater in pure fats and oils than in water (86) and blood (130), greater amounts of N_2 stored in lipid tissues can wash out later (120). Measurements of end-tidal N_2 concentrations during O_2 breathing shows that respiratory N_2 elimination in an exponential decay reflects phases of the N_2 release from various tissue compartments (89). The schematic representation on Fig. 1 illustrates the N_2 washout from multiple compartments; slow tissue compartments are illustrated by darker purple, reflecting their greater N_2 content than fast tissues (lighter purple) after the oxygen prebreathe. Based on the exponential process responsible for the N_2 respiratory elimination curve, an approximation of multiple straight lines (semilogarithmic plot) for various body compartments (115) can be suggested as follows (89): *1*) a rapid phase with a respiratory N_2 elimination half-time of about 1–5 min, corresponding to the N_2 release from highly perfused tissues such as brain, heart, liver, etc.; *2*) a middle phase with a half-time of about 12–15 min, probably reflecting N_2 given out by muscles; and *3*) a slower phase with a 110- to 220-min half-time, probably from fat. The calculated body fat and muscle mass were in agreement with the surface area under their respective fraction of the N_2 elimination curve (89). Clearly, the decompression stress and whether the tissue

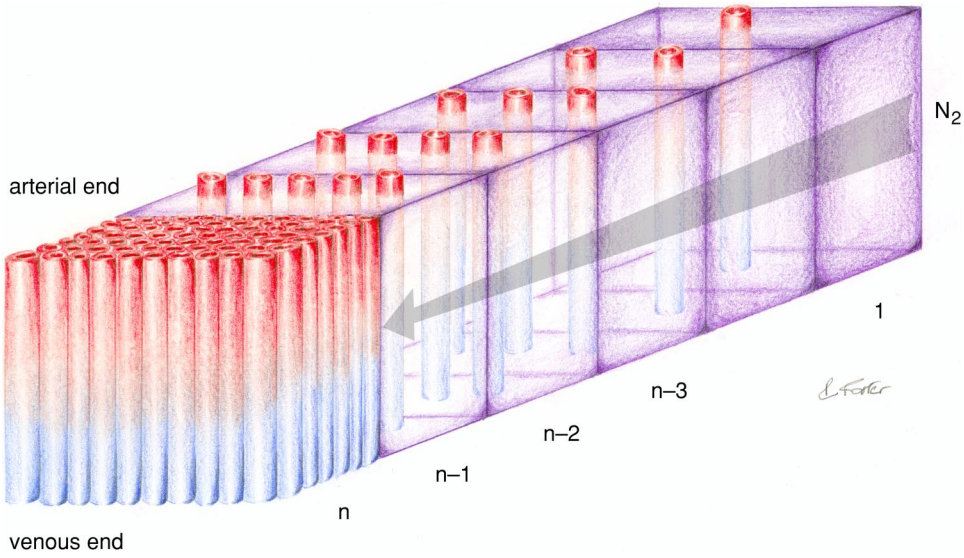


Fig. 1. Schematic representation of nitrogen washout from *n* tissue compartments during the oxygen prebreathe, the decompression, and the altitude exposure. Slow tissues (fat) with a low capillary density have long N_2 elimination half-times, whereas highly perfused tissues have a short half-times. N_2 respiratory elimination reflects phases of the N_2 release from various compartments and follows an exponential decay. [Illustration drawn by P. P. Foster.]

is aqueous or lipid regulate the amount of excess gas still available to form bubbles (120). Therefore, a high body fat content is likely to be a factor of greater susceptibility of DCI occurrence (2, 89, 90, 134). A greater weight may also be related to a greater amount of lean mass; this situation can be associated with another mechanism for bubble production. A larger muscle mass may allow a greater muscle tension and generate internal pressure differentials resulting in cavitation potential within connective tissues, further promoting bubble formation (134).

SKELETAL MUSCLE EXERCISE AND BIOMECHANICS: POSITIVE AND NEGATIVE IMPACT

A growing body of research indicates that skeletal muscle exercise and/or movement definitely affect(s) the washing out of N_2 from tissues but may also impact gas micronuclei, bubble formation, or the biochemical reaction to bubbles. Landmark reports are converging to suggest that the underlying mechanisms of bubble formation or suppression are highly sensitive to the fine-tuning of exercise/and or movement parameters easily measurable such as workload, oxygen consumption, duration, timing relative to decompression phase, and limbs and muscle groups involved. However, questions can be raised whether other parameters such as type of muscle contraction (eccentric or concentric), torque, and velocity may influence some decompression processes such as cavitation and micronuclei formation. Several potential mechanisms induced by aerobic endurance training may be involved in the tolerance to decompression. The response to exercise and movement is multifaceted, and some of the mechanisms involved are not amenable to experimental verification. Because the physical aggression from bubbles is shared both by hypobaric and hyperbaric exposures, we are assuming that biochemical pathways triggered by those decompressions should be on common ground. Therefore, we are referring to the experience from diving that might apply to altitude, and we are going to focus on potential effects of exercise and nitric oxide (NO) on decompression physiology.

Endurance aerobic training or a single bout of aerobic exercise? First, endurance training by the increase of muscle vs. body fat may have reduced the total N_2 content in adipose tissues and thus the potential N_2 release from supersaturated tissues during decompression (109). Second, endurance training also increases the capillary density in muscles (6) and the vascular flow capacity of fast-twitch glycolytic muscle tissue (87). Such an augmented microcirculation improves the washing out of N_2 from tissues into blood by decreasing N_2 tension in a larger number of individual capillaries (109). An increased density of capillaries provides collateral vasculature and opportunities to ameliorate the effects of a capillary occlusion by a bubble (109). Third, the positive effect of aerobic endurance training on the cardiovascular system, such as increased myocardial contractility, cardiac hypertrophy, stroke volume, maximal cardiac output, and cardiac reserve, enhances the N_2 respiratory elimination (142). Aerobic endurance exercise and training by 28 daily 1-h treadmill exercise sessions dramatically reduced the incidence of DCI in mice and was not caused by the reduced body weight and body fat of trained mice (109). However, without any previous aerobic endurance training, a single bout of aerobic exercise lasting 1.5 h the day before decompression reduced the amount of bubbles in the right ventricle and pulmonary artery of rats and the incidence of DCI (142). The experiment was replicated in humans performing a 40-min exercise alternating periods at 90% and 50% maximal heart rate 24 h before hyperbaric decompression, decreasing the number and the volume of bubbles detected in the pulmonary artery (46). On one hand, it is unlikely that a single short exercise would be sufficient to significantly improve the capillary density and other cardiovascular benefits from exercise. On the other hand, this improvement would not be caused by the effects of acute exercise effects since decompression follows 20–24 h later. In this case, the underlying mechanism is probably related to a mechanism independent of direct N_2 elimination enhancement. Fourth, Wisloff and Brubakk (142) suggested that another mechanism unrelated to the cardiorespiratory adaptation following aerobic training but related to a short single bout of exercise was sufficient to reduce bubbling and DCI. These authors suggested that this preventive effect might have mediated via a reduction of density of gas micronuclei. Interestingly, the same type and intensity of exercise that reduces bubble formation when performed 20 h before a dive neither promotes nor reduces bubble formation if performed 30 min before a dive (16).

A role for nitric oxide? The same group suggested that nitric oxide (NO) plays a significant role in bubble formation (143). The administration of a nonselective inhibitor of NO synthase (NOS), N^G-nitro-L-arginine methyl ester (L-NAME), caused significant increase in bubble formation and decrease in survival rate of sedentary rat (143). It was suggested that endothelial NOS isoform (eNOS) had also probably been inhibited in this experiment; eNOS is a membrane phospholipid-associated enzyme that has an important role in regulation of the vascular tone and in inhibiting platelet adhesion or aggregation (126). Clearly, several NO-mediated mechanisms may mitigate potential pathways to bubble formation and DCI incidence. One interpretation of the results is that NO affects the hydrophobicity of the endothelial wall, which reduces the stability and density of nuclei adhering to the surface (49, 143). Another striking result is that the optimal time for the prescription of 1.5-h endurance exercise to providing maximum protection against bubble formation and DCI was ~20 h before decompression (144). Furthermore, administration of isosorbide mononitrate, a NO donor, 20 h or 30 min before decompression provided the same level of protection against bubbles and DCI as the latter prescription of exercise bout 20 h before decompression (144). The experiment has been replicated in humans with a NO donor, nitroglycerine, administered 30 min before the dive, which reduced potential bubble formation for the next hours (49, 50). Nitroglycerine is considered as short-lasting (15 min), and its effects on the vascular tone may not provide a consistent explanation for the delayed action on prevention of bubble formation. Mollerlokken et al. (91) bring about additional evidence of vascular prevention of vascular bubble formation in pigs by administration of the same short-acting NO donor 30 min before a saturation dive inducing significant levels of tissue N_2 supersaturation. The mechanism of action could be due to NO-induced alterations of endothelial properties, which may lower the hydrophobicity of the vascular endothelium and induce a long-lasting impediment to bubble formation (114, 143, 144). However, NO effects on the inhibition of platelet aggregation and leukocyte adhesion cannot be

ruled out as potential contributors (92). It is possible that an increase in NO might have also been activated by the exercise before decompression. Furthermore, the authors of the last report suggested that exercise upregulated the gene expression of eNOS and inducible NOS (iNOS), leading to the increased NO release (144). However, we are still left without any explanation about the lack of efficiency of exercise in this experiment only a few hours (10 h, 5 h, and 30 min) before decompression despite the probable NO increase in these exercising rats (16, 144). The logical question is whether another unscheduled spontaneous exercise- or movement-induced mechanism timed shortly before decompression precluded the protective effect of exercise-induced release of NO on bubble formation and increased altitude DCI incidence.

The gas micronuclei conundrum and the type of contraction: a new hypothesis? Reports in animals (18) involving violent exercise and in humans (43) performing deep knee squats show that exercise performed immediately before altitude decompression favors bubble formation. A major difference with other exercises such as concentric cycling is that deep knee squats have an important eccentric component potentially disruptive to the sarcolemma and a level of soft tissue damage (62, 94, 140). Disruptions or damage may have exposed hydrophobic surfaces and/or facilitated viscous adhesion or cavitation generating gas micronuclei. Vigorous or ballistic exercise to the point of muscle soreness before decompression was reported to increase the risk of DCI (18, 73). A striking finding was that performance of exercise with a lag time greater than 1 h before decompression does not induce such an increase in bubble formation (43). Because gas micronuclei are not amenable to in vivo experimental observation, their lifetime cannot be verified. However, it is possible that short-lived gas micronuclei may have also formed during the other test conditions, i.e., 1 and 2 h before decompression, and already disappeared during the seated resting period before decompression began (43).

The gait and the standing posture: a puzzling cornerstone? During ground-based experiments, in the altitude chamber, the effect of resting, by expressly avoiding walking or striding and the standing posture, sometimes called in this context "adynamic state" ("adynamia") (37) of the lower limbs, brings about another puzzling cornerstone in hypobaric decompression. In the report by Conkin and Powell (37), this period of restriction of lower body involvement in the gait or standing applied to the O_2 prebreathe phase for all subjects and was extended to the decompression and altitude exposure for one subset; the hypothesis was tested with a control group allowed to walk. The restriction of walking or standing significantly reduced the incidence and increased the latency time for the first onset of Doppler-detected bubbles and DCI symptom (37); when (pain-only) symptoms occurred, they affected upper as well as lower limbs with a distribution similar to that of walking subjects. Another report focusing on DCI occurrence (133) showed that joint-pain DCI was less prevalent in the lower body than in the upper body in subjects restricted to walking ("nonambulatory") during hypobaric exposures and the opposite during "ambulatory" exposures; the overall DCI incidence was unchanged in the two groups. The contrasting results between the two latter studies may be explained by different working altitude pressures and different O_2 prebreathe. The essential premise of unverified underlying mechanisms of decompression concerns the control of the nucleation process before decompression and N_2 tissue supersaturation. The generation of de novo micronuclei may take only a few minutes, and in the presence of a substantial tissue supersaturation the critical radius for bubble growth may be overcome. Underlying mechanisms of hypobaric decompression may be blunted by the complex interactions between *1*) tissue N_2 supersaturation; *2*) exercise-induced enhancement in N_2 elimination via an increase of cardiovascular and respiratory response; *3*) aerobic endurance training; *4*) short aerobic exercise before decompression; *4*) effect of NO; *5*) type of contractions involved; *6*) effect of biomechanical characteristics of the movement; and *7*) strict inactivity of the limbs. The divergent reports from well-designed studies reflect the complexity and the interferences of mechanisms involved. A rigorous examination of timing, intensity (32), and type of exercise or exercise-related parameters may provide a clearer picture of the gas micronuclei regulation, N_2 elimination, bubble growth, and DCI incidence.

The Russian ground-based suited experiments and biomechanics considerations. Using a large sample size of subjects ($n = 312$), the incidence of DCI was considerably reduced in subjects donning the EVA space suit ($n = 130$) vs. short-sleeves subjects during decompression to $P_B = 24–40$ kPa in a hypobaric chamber (11). The authors suggested that the restriction of movement with a decreased angular velocity would have reduced the opportunity of cavitation and thus bubble formation during motion. Another experiment replicated on a small scale showed the same trend albeit the number of subjects did not reach statistical significance since it was primarily designed to study the feasibility of Doppler in-suit monitoring during EVA missions (10). This effect seemed to be independent of the oxygen consumption, which was the same in the suited and unsuited groups.

A PROTECTIVE ROLE FOR CONCENTRIC EXERCISE?

Altitude decompression. In a milestone report, Webb et al. (132) demonstrated that a 10-min aerobic submaximal bilateral arm and leg exercise at 70–80% peak oxygen consumption $\dot{V}O_{2peak}$ on a dual-cycle ergometer during oxygen prebreathe ($F_{IO_2} = 1$, 60 min total) before decompression significantly decreased the incidence of DCI at altitude ($P_B = 30$ kPa, $F_{IO_2} = 1$). The control group did not have the 10-min exercise regimen; a third group performed a 10-min exercise during a 15-min O_2 prebreathe. Therefore, it appears that exercise involving concentric contractions such as cycling may provide enhanced N_2 washout from tissues without increasing the population of micronuclei. Another landmark was the design of the 2-h oxygen prebreathe reduction protocol (PRP) and its implementation in a multicenter trial (24, 63, 64, 128). The 10-min PRP exercise included continuous incremental phases on a dual-cycle ergometer up to a plateau of ~75% $\dot{V}O_{2peak}$ with only a light arm work rate (24, 63, 145) compared with the study of Webb et al. (132). The restriction to walk and to stand applied to the whole experiment, including prebreathe, decompression, and altitude exposure (24, 63). Twenty four minutes of light activity simulating the space suit preparation was added. The decompression profile is illustrated in Fig. 2. No occurrence of altitude DCI was reported, and VGE were detected in 28% of subjects; the PRP was associated with a low

6% incidence of the highest bubble grade (IV) (24). The PRP, adapted for space missions (60, 145), was approved for flight and has been successfully used on the International Space Station. An interesting report from Balldin et al. (8) provides further insight into the interactions between three mechanisms: *1*) tissue N_2 supersaturation during decompression, *2*) exercise-enhanced oxygen prebreathe, and *3*) absence of stride or standing posture. The test conditions were *1*) 3-h strict supine position, including 60 min O_2 prebreathe (P_B = 101.3 kPa, $F_{I_{O_2}}$ = 1) before decompression to 30 kPa ($F_{I_{O_2}}$ = 1); and *2*) concurrence of a 10-min exercise of bilateral leg cycling and arm cranking on a dual-cycle ergometer at 75% of $\dot{V}_{O_{2peak}}$ performed during the O_2 prebreathe. Control subjects undertook the same protocol except for the supine position. No difference was found in the incidence of DCI; Doppler-detectable bubbles occurred more frequently in controls than in supine subjects (81% vs. 51%). Clearly, the strict supine position maintained before prebreathe, during the exercise-enhanced prebreathe and at altitude, did not appear to reduce the incidence of symptoms (8). Two overwhelming factors seem to have influenced the incidence of DCI: *1*) the level of N_2 supersaturation, and *2*) the enhancement of tissue removal and respiratory elimination of N_2 from the 10-min exercise administered during prebreathe.

The hyperbaric decompression experience. In hyperbaric decompression, the exercises tested were not as definite as those for altitude. Oftentimes hyperbaric exposures involved a mixture of various exercises. However, authors reported the beneficial effect of cycling exercise during the decompression phase of a dive (19, 75). Two reports indicated that cycling exercise with the legs and paddling or light weight lifting with the arms during decompression to surface (73), but not during bottom phase, protected against bubble formation especially severe bubbling (74). Henry (70), with a similar weight-lifting experimental procedure at altitude, noticed that the incidence of altitude DCI increased with the augmentation of the total angle that subjects were achieving with the articulation. This experiment also suggests that during the bottom phase, the exercise-induced increase in minute ventilation, pulmonary capillary blood flow, cardiac output, and muscle blood flow, the N_2 exchanges between tissues and lungs did not exhibit a trend toward the increase of N_2 tissue washout due to the high $P_{I_{N_2}}$ at the bottom (73, 74); there is probably an acceleration of both N_2 tissue washout and wash-in during this phase with probably more N_2 tissue wash-in due to the equilibration of $P_{I_{N_2}}$ with the N_2 tension in pulmonary capillary blood and in tissues, Pt_{N_2}. In contrast, during decompression, N_2 tissue washout from fast tissues with short half-times (5–10 min) is favored by the moderate intermittent exercise and the lowering of $P_{I_{N_2}}$ (73, 74). Indeed, a mild 3-min leg exercise (underwater swimming) at 30% of maximal oxygen consumption $\dot{V}_{O_{2max}}$ during the decompression phase of a dive was sufficient to reduce the number of detectable bubbles in the right heart and the pulmonary artery (48); non-weight-bearing activities such as swimming do not usually include eccentric contractions (95). Furthermore, a 10-min leg exercise on a cycle ergometer at up to 85% $\dot{V}_{O_{2max}}$ performed after the dive reduced postdive bubble formation (47).

DOPPLER-DETECTABLE BUBBLES AND DCI

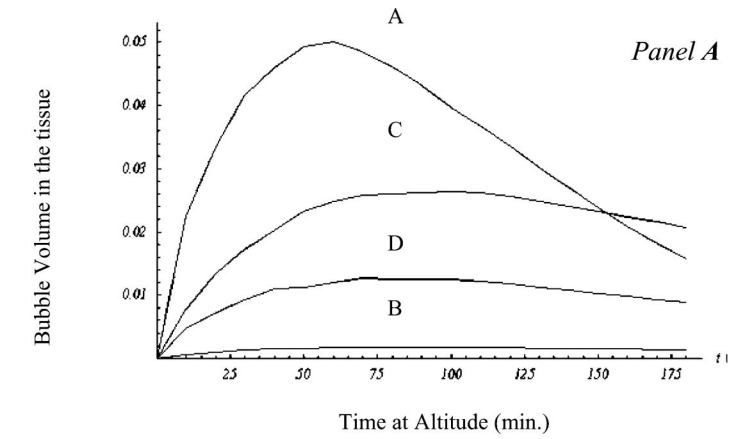
The symptoms of altitude DCI range from mild, musculoskeletal pain of "bends" to serious neurological complications (81, 110). However, mechanisms linking bubble formation with symptoms are still not completely understood, although it is generally agreed that substantial bubble formation can occur without symptoms (51). Doppler-ultrasound techniques and echocardiographic imaging to detect a moving gas phase such as gas emboli in the four chambers of the heart or the pulmonary artery have been widely used in altitude and diving physiology (7, 9, 35, 38, 39, 44, 73, 74, 102). Absence of detectable VGE is a powerful indicator of decompression safety (38, 52). However, "silent bubbles," not causing patent clinical DCI, may cause subclinical damage (96, 97). Efforts have been made to correlate the physics of evolving gases as a decompression dose to the perception of altitude pain-DCI symptoms (34). The presence of VGE is not highly associated with the subsequent occurrence of DCI symptom (38, 83, 98). There may be several reasons for the relatively low predictive positive value of Doppler detection, e.g., "stationary" microbubbles (83), undetected by Doppler-ultrasound, which may cause clinical manifestations of pain symptoms (80). However, DCI was rarely (2%) (38) or infrequently (23%) (98) associated with the absence of VGE but not often correlated with the presence of a large volume of VGE (high grade of bubbling) (38). Doppler ultrasound has therefore a greater utility in excluding DCI than confirming its presence (84). In a retrospective study (9) of a large number of exposures, DCI with neurological symptoms involving the central nervous system was associated with detectable VGE in only 55% of the cases; the association was stronger for symptoms not involving a neurological component (84%). For high bubbling grades, the sensitivity of the Doppler-ultrasound decreased and the positive predictive value increased in predicting the occurrence of all altitude DCI symptoms (82). A delayed onset of VGE

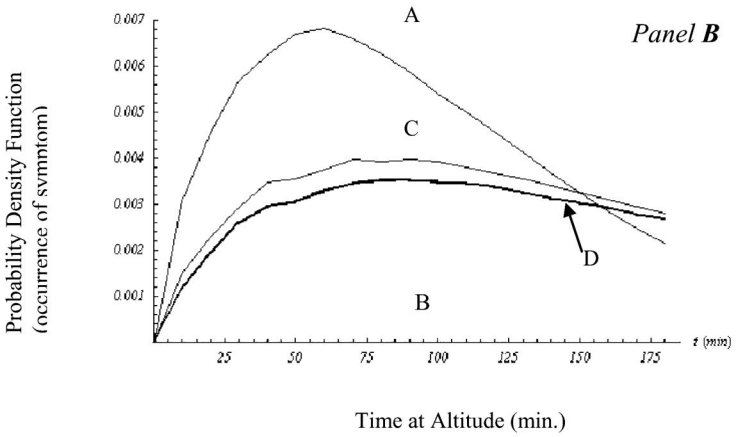
Fig. 2. Simulation of the bubble volume (*panel A*) in a region of tissue and probability density function (pdf; *panel B*) of failure [occurrence of decompression illness (DCI)] at altitude for various staged oxygen prebreathe procedures commonly used in the Space Program: *procedures A, B, C,* and *D* (58, 59). The duration of the oxygen prebreathe increases from *A* to *D*. Prebreathe *procedures B* to *D* include a staged decompression to the total pressure of gases in the breathing medium or barometric pressure (P_B) = 70.3 kPa (10.2 psia) and $F_{I_{O_2}}$ = 0.265. The 2-h prebreathe reduction protocol (PRP), illustrated by *procedure B* (diagram not to scale), significantly reduced the duration of the prebreathe by adding a 10-min cycling exercise [P_B = 101.3 kPa, fraction of inspired O_2 ($F_{I_{O_2}}$) = 1] before the ascent to the first stage (P_B = 70.3 kPa, $F_{I_{O_2}}$ = 0.265), followed by a switch in the breathing medium (P_B = 70.3 kPa, $F_{I_{O_2}}$ = 1) before the ascent to final altitude exposure (P_B = 30 kPa, $F_{I_{O_2}}$ = 1) (24, 63). The initial growth is followed by a decay, reflecting the N_2 washout from tissues while breathing $F_{I_{O_2}}$ = 1 at altitude; N_2 lost by the tissues will no longer be available to diffuse into bubbles. Therefore, the volume of bubbles is reduced by long O_2 prebreathe procedures. The pdf defines the probability that an individual fails, or manifests DCI at a certain time, during a short interval of time (≈instantaneous) (58, 79, 83). The pdf curve reaches a maximum, then decreases. The risk can also be assessed with the cumulative distribution function (not shown) or cumulative incidence of DCI which is thus increasing with time until the end of the altitude exposure (35, 36, 38, 103). The decay in the pdf probably also reflects the loss of N_2 by tissues while breathing $F_{I_{O_2}}$ = 1 at altitude. For the PRP, no incidence of DCI was reported (24) and the pdf curve would have been a straight line superimposed on the *x*-axis. [Adapted from previous depictions of original conceptual model (58); *panel A* has no unit on the *y*-axis, and no estimation based on actual data has been attempted in either *panel A* or *B* of the current figure.]

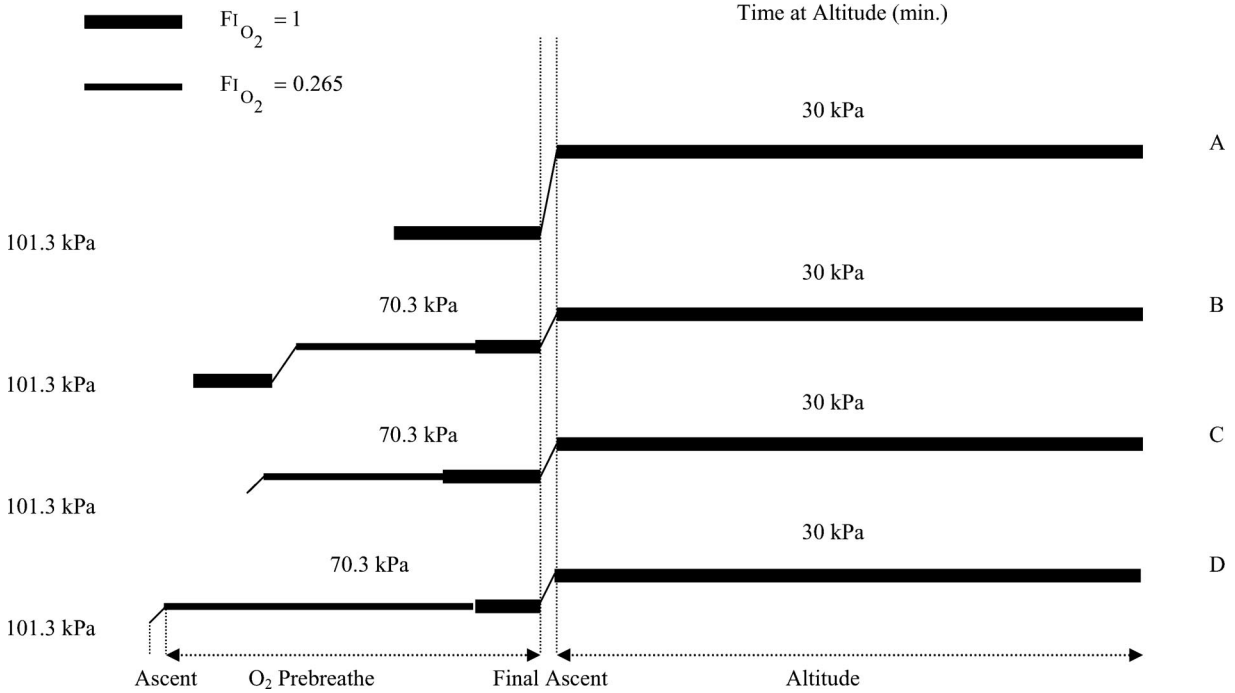
was correlated with a significant reduction in the risk of symptoms (79).

POTENTIAL ARTERIALIZATION OF VGE

Pulmonary capillaries normally trap VGE (27, 28), and the gas contained inside would diffuse into the alveoli for further elimination in the expired fraction. The effectiveness of the pulmonary vasculature for bubble filtration can be overwhelmed for large volume of VGE, and the arterial spillover may occur (27, 28). Gas emboli from venous sites may be arterialized via the pulmonary transcapillary route (25), intrapulmonary arteriovenous shunts, and through intracardial







septal defects (28, 56). The patent foramen ovale (PFO) may allow VGE to cross from the right to the left atrium and provides one potential mechanism of the paradoxical systemic embolization of bubbles during decompression (93, 141) as illustrated on Fig. 3. VGE in the pulmonary circulation can result in both mechanical obstruction and vasoconstriction (26–28, 31). The subsequent pulmonary hypertension and increase in vascular resistance may cause an increase in the right atrium pressure relative to left atrium pressure, which may result in a right-to-left shunting through a PFO, if present (26, 28, 31). However, even with VGE, the interatrial pressure gradient, and hence flow, may not always be reversed (31). Furthermore, during common altitude exposures, the amount of decompression-induced VGE at altitude may not be sufficient to cause a reversal of the interatrial left-to-right normal pressure gradient and subsequent right-to-left shunting through a PFO (44, 56, 107). VGE seemed more likely to traverse a PFO than to travel through the pulmonary vasculature (127). However, especially with VGE overloading in the pulmonary vasculature, the normal filtration capability of the lungs can be exceeded and arterialization can occur via transpulmonary passage or a PFO (102). Arterialization of gas bubbles may

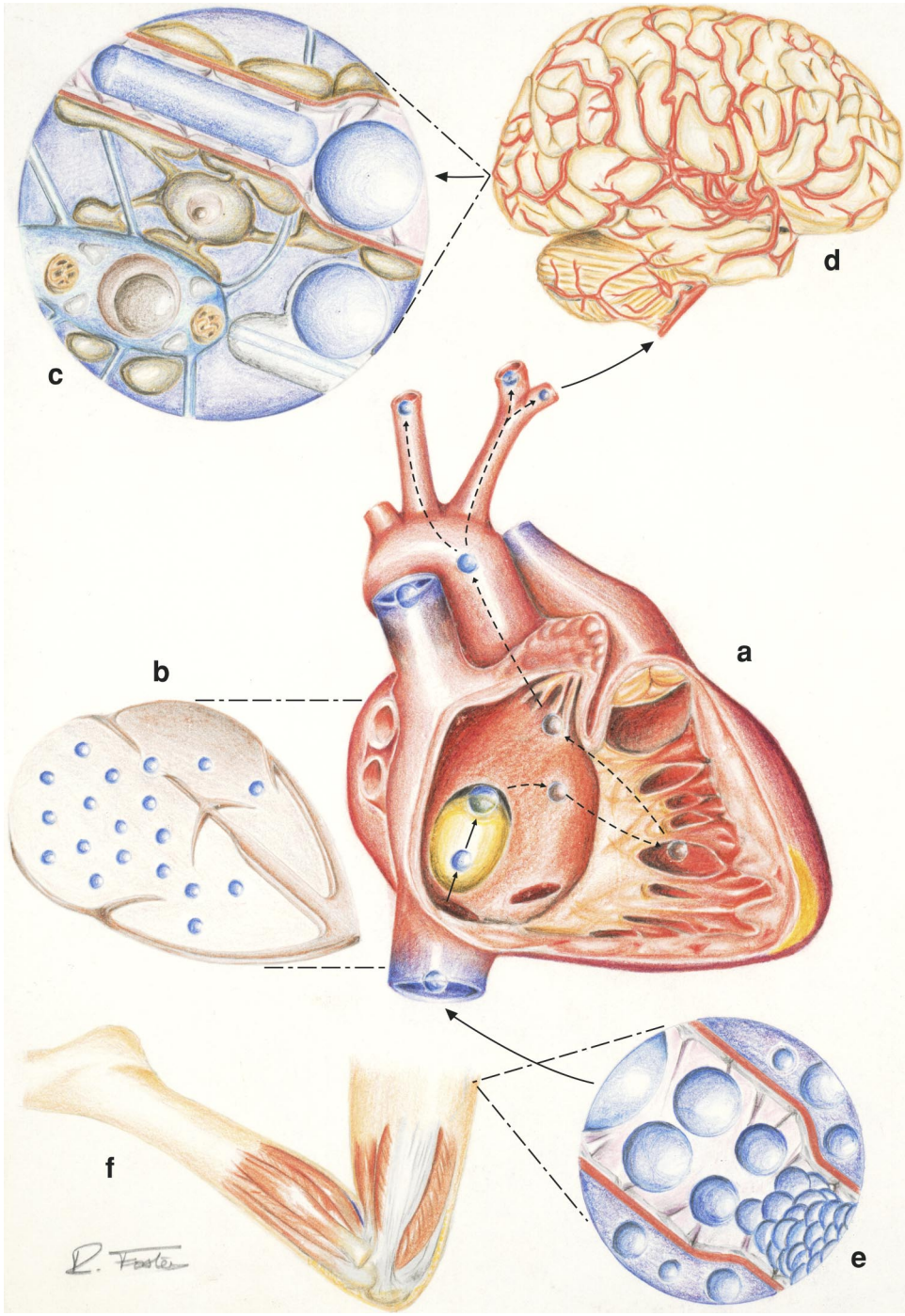


Fig. 3. Schematic representation of the mechanism of arterialization of bubbles (*a, b, c, d*) and the role of exercise potentially positive or negative in preventing decompression outcomes (*e, f*). Note that bubbles can be intravascular or extravascular. [Illustration drawn by P. P. Foster.]

lead to neurological symptoms (93). The possibility of serious DCI symptoms with VGE overloading raises broader issues. The necessary conservative oxygen prebreathe procedures lower the risk of such high bubbling grades and of such serious symptoms during altitude exposures.

MICROGRAVITY AND ALTITUDE DECOMPRESSION: THE PARADIGM

Although ~75% of U2 pilots experienced altitude DCI during their career (14, 104), no case has been reported during actual EVAs on orbital flights. According to the level of oxygen prebreathing and decompression, ground-based models predicted a considerably higher incidence of DCI than that actually observed in microgravity (35, 36, 38, 103, 124). The paradigm for such mitigation in the absence of gravity is unknown. Given the lack of consensus, this review obviously reflects our individual perspectives. Fundamental questions were raised about the role of microgravity in altitude decompression physiology and biology. With so many mechanistic targets, the task to shed light to current bottlenecks in this field is challenging, and we will attempt to provide a summary of unresolved questions and potential future directions for research as follows. First, does adaptation to microgravity enhance N_2 tissue washout? Second, does microgravity reduce bubble formation possibly via a reduction in density of gas micronuclei? We do not have in-flight N_2 respiratory washout measurements available, and therefore it is difficult to assess whether the changes in microgravity will facilitate N_2 washout. In microgravity, increase in heart size, left-ventricular diastolic volume, stroke volume, and cardiac output (139), albeit with a decrease in central venous pressure (21), might tend to facilitate N_2 tissue washout. The minute ventilation was decreased but alveolar ventilation was slightly impaired by only 4%, and the ventilation-perfusion inequality was not altered by the absence of gravity (108). Therefore, it is unclear whether microgravity-induced changes in the pulmonary function influence positively the N_2 washout and, if so, to what extent. Conversely, it is likely that the effects of absence of gravity on the musculoskeletal system may impact the decompression physiology as follows. Loaded eccentric contractions occur during normal daily activity but are absent in the non-weight-bearing environment of microgravity (78). Accordingly, observations reproduced in multiple laboratories indicated that pre- or per-decompression exercise produced an increase in bubble formation and/or DCI symptoms (18, 43, 70, 100); all these exercises seemed to have involved eccentric contractions. One report (100) involved dynamic exercises on a weight stack machine and also a procedure with high-torque isometric exercise to maximal voluntary contraction. [Isometric contractions have also been shown to generate muscle membrane damage via excitation-induced influx of Ca^{2+} (61).] Therefore, tissue damage, known to induce bubble formation (18) via a possible increase in micronuclei density, may also be implicated during isometric contractions. Furthermore, absence of DCI in microgravity strengthens these observations. Further evidence was also highlighted by the reduced incidence of DCI when donning an exoskeleton such as the space suit during altitude decompression (10, 11). The restriction of movement and the suit stiffness probably resisted the occurrence of detrimental movement such as forced lengthening. Indeed, an association between oxygen uptake and bubble formation or DCI occurrence has also never been conclusive. It is therefore possible that dual effects of exercise on bubble generation and occurrence of DCI may depend on the contraction type. Multiple studies reported evidence about the protective role of concentric cycling exercise at every stage pre-, per-, and postdecompression in reducing bubbling and DCI (8, 24, 63, 64, 128, 132). During altitude exposures, it appears that concentric cycling exercise performed during oxygen prebreathe enhances N_2 tissue washout without causing an increase in the amount of VGE and DCI incidence (24, 132). This allows a reduction of prebreathe time and a saving of critical operational time (63, 128).

CONCLUSIONS

Research over the past decade has established the physiological importance of exercise as modulator of bubble formation and DCI during altitude decompression and its dual role, either protective or detrimental. Skeletal muscle exercise and movement affect N_2 washout from tissues but may also impact gas micronuclei, bubble formation, or the biochemical reaction to bubbles. Whole body exercise involving concentric contractions such as cycling provides enhanced N_2 washout from tissues during the oxygen prebreathe and hence allows a reduction of prebreathe time. This concentric exercise does not appear to increase the population of micronuclei in critical tissues. Several studies have demonstrated the existence of another mechanism related to a short exercise albeit unrelated to the N_2 washout or the cardiorespiratory adaptation following aerobic exercise training. Experimental evidence indicates that there is an exercise-induced protective effect mitigating potential pathways to bubble formation and DCI incidence via the release of NO and possibly via a potential reduction of density of gas micronuclei. NO may affect the hydrophobicity of the endothelial wall, which reduces the stability and density of nuclei adhering to the surface. In contrast, observations reproduced in multiple laboratories indicated that pre- or per-decompression exercise produced an increase in bubble formation and/or DCI symptoms; all these exercises seemed to have involved eccentric contractions except for one experiment including high-torque isometric contraction. Eccentric contraction can adversely affect the sarcolemma and generate a level of soft tissue damage. Tissue damage, known to induce bubble formation, may expose hydrophobic surfaces and/or facilitated viscous adhesion or cavitation generating gas micronuclei. Conversely, occurrence of DCI is precluded within the confined space suit itself or in the non-weight-bearing microgravitational environment; in both settings loaded eccentric contractions are minimized or absent. This highlights the importance of unanswered questions about the underlying mechanisms of altitude decompression: What pathways are activated or inactivated during eccentric or concentric muscle contractions, and physical inactivity? What is the influence of lunar or Martian gravity on those pathways? Clearly, these queries can only be answered by continued research.

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