Undersea Biomedical Research, Vol. 5, No. 3, September, 1978

Decompression advantages of trimix

T. E. BERGHAGE, C. DONELSON, IV, and J. A. GOMEZ

Behavioral Sciences Department, U.S. Naval Medical Research Institute, Bethesda, MD 20014

Berghage, T. E., C. Donelson, IV, and J. A. Gomez. 1978. Decompression advantages of trimix. Undersea Biomed. Res. 5(3):233–242.—For saturation exposures, animal studies have demonstrated that breathing mixtures of multiple inert gases provide no more protection against decompression sickness than breathing mixtures of helium-oxygen. It has been suggested, however, that the differential gas-exchange characteristics of nitrogen and helium could provide a decompression advantage for short-duration dives, if the gases were mixed in the proper proportions. To evaluate this possibility, we exposed 700 albino rats to two pressure levels (7 and 16.2 ATA), five exposure times (5, 15, 30, 60, and 120 min), and five inert gas combinations (helium/nitrogen, percent: 0/100, 25/75, 50/50, 75/25, and 100/0). The oxygen partial pressures were kept constant at 0.51 ATA. During each pressure exposure five rats were exercised in a rotating cage. After the pressure exposures the animals were rapidly decompressed to a lesser pressure (1 or 4.9 ATA, depending on the exposure pressure) for a 30-min observational period. Oxygen partial pressure during the observation period was maintained at 0.2 ATA. The incidence of pain-only decompression sickness (bends) noted at the end of this period was the dependent measure. Results of these exposures suggest that the use of multiple inert gas combinations can facilitate decompression for short-duration dives. The optimum combination of inert gases is related to the exposure time ($P < 0.005$): the relative concentration of helium must be increased as exposure time is lengthened.

decompression sickness
decompression optimization

The use of multiple inert gas mixtures for reducing the decompression requirement after a hyperbaric exposure has been a topic of interest since it was first alluded to by Sayers and Yont in 1926. During initial tests with helium-nitrogen inert gas combinations, it was erroneously assumed that the two inert gases would act independently and that the decompression needed after breathing a 50/50 mixture of a diluent plus oxygen would be reduced by half. Momsen (1942) states that "This error led the British to report unfavorably on the possible use of helium and led . . . the U.S. . . . experimenters into serious trouble, which resulted in many cases of bends." At this point, the U.S. Navy Experimental Diving Unit adopted the policy of summing the partial pressures of all of the inert gases into a single component, which they called the "partial pressures of AOG (all other gases)." Calculations based upon this idea disregard any possible advantage of using multiple inert gases and probably err on the safe side. This conservative approach is still the method of choice today.

Two approaches to the use of multiple inert gases have been suggested: the serial presentation of single inert gases (Keller and Bühlmann 1965) and the simultaneous presentation of a combination of inert gases (Webster 1955). This paper will deal with the approach outlined by Webster.

The theoretical advantage ascribed to the use of multiple inert gases is based upon the differential saturation times for the inert gases involved. Webster states that the sum total of the partial pressures of the inert gases is the value of concern for the decompression theorist, but he contends that substantial advantage can be obtained by using the differential uptake and elimination times of the multiple inert gases. Both Webster (1955) and Keller and Bühlmann (1965) suggest that the speed at which a tissue saturates with a particular gas is inversely proportional to the square root of the molecular weight of the gas (Graham's Law) and is independent of the gas' solubility. Based upon these assumptions, Keller and Bühlmann published figures indicating that the saturation time for helium is about 2.65 times faster than that for nitrogen in the same tissue. These results suggest that heavy gases provide an advantage in dives of short duration, but would tend to extend the decompression time after a long exposure. Just the opposite would be true for light gases such as helium. If this principle is correct, there should be an optimal combination of heavy and light gases; gases and proportions would depend upon dive duration.

Two studies have investigated the possible advantage of using multiple inert gas combinations for saturation dives (McMahon and Lambertsen [unpublished Univ. of Pa. report] 1957; Wex, Long, and Flynn 1971). Both of these studies found that the incidence of decompression sickness was lower for those mixtures containing helium than for those in which nitrogen was the only diluent gas. Wex et al. (1971) reported that a steady decrease in the incidence of decompression sickness was associated with the use of increasing fractional concentrations of helium. This relationship held true until the diluent consisted of as much helium as nitrogen, after which no change in the incidence could be detected. Essentially the same results were obtained in the study by McMahon and Lambertsen. Thus, these studies indicated that the use of an inert gas with a low molecular weight for decompression after saturation dives is advantageous.

Some initial work on the effects of multiple inert gases on decompression after a subsaturation dive was reported by Workman (1963) and by McMahon and Lambertsen (1957). Working with albino guinea pigs, McMahon and Lambertsen found no decompression advantage with a nitrogen-helium-oxygen breathing mixture compared to a helium-oxygen mixture, regardless of the exposure time. This study, however, presents several procedural questions: neither exposure pressure nor oxygen partial pressure were held constant, and both of these variables have been shown by Berghage, Conda, and Armstrong (1973) to be critical. Human data reported by Workman (1963) indicated that the length of the decompression after a subsaturation dive could be substantially shortened by using more than one inert gas in the diluent. The following items therefore summarize our preinvestigation knowledge of the decompression risk associated with breathing multiple inert gases:

1. For saturation exposures, the lighter the inert gas used, the better the results. The presence of a second inert gas in the diluent provides no advantages.
2. For some subsaturation dives, using a diluent consisting of as much nitrogen as helium produces better results than either of these inert gases by itself.

In the present study we evaluated these two points and attempted to determine the relationship between time and the optimal concentration of helium and nitrogen.

METHOD

Subjects were 500 male and 200 female albino rats (NMRI:0[SD], Sprague-Dawley derived). Mean and standard deviation of their free-feeding weight at the time of the experiment were 291 ± 32 g.

All pressure exposures were made in a Bethlehem Model 1836 10-HP chamber with a volume of approximately 170 liters. Chamber atmosphere was monitored with a Beckman Model F-3 paramagnetic oxygen analyzer; oxygen partial pressure was maintained at 0.51 ATA during the compression and time at maximum pressure. Carbon dioxide levels were not monitored because previous exposures had demonstrated that the chamber life-support system kept the carbon dioxide level well below 0.2% surface equivalent. Chamber pressure was monitored with a 0- to 2000-fsw Heise gauge and maintained within ±2 fsw of the specified pressure. The temperature in the chamber during the exposure was kept at 30° ± 2°C.

During each pressure exposure, five rats were exercised at a rate of 5 rpm (3.33 m/min) in a 22.4-cm diameter rotating cage. The experimental design called for four pressure exposures (20 rats) for each experimental condition. Two different pressure levels (7 and 16.2 ATA) and five different diluent gas mixtures (0/100, 25/75, 50/50, 75/25, and 100/0 percent helium to nitrogen) were combined for selected exposure times (Table 1). Male rats were used during the 7-ATA exposures and females during the 16.2-ATA exposures. Using different sexes was necessary because there were not enough male rats. At the lower pressure level, five different exposure times were used: 5, 15, 30, 60, and 120 min. At the higher pressure level, only two exposure times were used: 15 and 30 min. Directions for procedures during the trimix exposures were:

1. Compress the chamber to 1.3 ATA (10 fsw) with oxygen to establish the Po_2 at 0.51 ATA.
2. Compress the chamber at the rate of 1.82 atm/min (60 fpm) to 2.92, 4.55, or 5.87 ATA with helium to establish the proper helium concentration.
3. Compress the chamber at the rate of 1.82 atm/min (60 fpm) to 7 ATA with nitrogen.
4. Remain at 7 ATA for either 5, 15, 30, 60, or 120 min.
5. Ventilate the chamber in the last 60 s of the bottom time to raise the oxygen level to 20% for surfacing.
6. Decompress to the surface in 17.7 s (0.34 atm/s).
7. Observe the exercising animals for 30 min, and record time of onset of symptoms.

For the nitrogen-oxygen exposures, step 2 in this sequence was omitted. For the helium-oxygen exposures, directions for steps 1 through 3 were altered as follows:

1. Ventilate the chamber for 5 min with oxygen to remove the 0.79 ATA of nitrogen.
2. Compress to 3 ATA with helium.
3. Ventilate the chamber with helium until the oxygen is at 17% (0.51 ATA).

For the exposures made at 16.2 ATA, the same step-by-step procedure was used, but with different absolute values for the compression stops. The abrupt decompression after the 16.2-ATA exposure was to a pressure of 4.9 ATA (observation pressure); the elevation of oxygen percentage was between 3% and 4% before decompression.

Shifting the oxygen percentages (step 5 above) should have had a minimal effect upon the results. All pressure exposures were handled in the same way so that this effect, if any, was uniform. Also, half times for the rat are long enough (8 min for helium and 22 min for nitrogen) so that 60 s of increased oxygen should only alter total gas content by about 10%. Oxygen partial pressure was maintained at 0.2 ATA during the observation period.

TABLE 1
EXPERIMENTAL DESIGN CELLS DISPLAYING INCIDENCE OF DECOMPRESSION SICKNESS, TIME OF SYMPTOM ONSET, AND MEAN ANIMAL WEIGHTS (20 ANIMALS PER CELL)

Time, min	Descriptors*	Nitrogen/helium percentages 100/0	75/25	50/50	25/75	0/100
		7-ATA exposures				
	%	10	5	5	20	60
5	T	10.6	5.4	8.3	6.3	3.1
	W	292	253	243	227	214
	%	60	50	30	40	55
15	T	3.1	2.1	7.4	7.3	8.5
	W	309	317	261	257	343
	%	90	85	65	60	60
30	T	2.6	2.2	5.7	5.1	8.6
	W	323	339	262	241	314
	%	95	85	70	80	65
60	T	3.6	3.2	3.7	5.2	4.3
	W	253	345	249	253	278
	%	85	90	90	95	90
120	T	2.5	2.7	4.5	3.9	7.1
	W	305	300	397	391	312
		16-ATA exposures				
	%	20	0	20	25	25
15	T	14.3	–	10.2	7.3	7.2
	W	239	217	241	260	232
	%	50	50	50	45	50
30	T	9.0	9.4	9.7	9.7	8.9
	W	235	259	226	226	241

*% = Percentage of animals displaying signs of decompression sickness; T = average time (min) to onset of symptoms; W = mean weight (g) for 20 animals.

At the end of the observation period (step 7), the behavior of each animal was evaluated on a three-point scale: 1) normal walk; 2) abnormal walk, paralysis, or convulsions; 3) tumbling in the cage. The tumbling in the cage classification was used because the observation pressure levels were not all at 1 ATA; consequently, the rats were isolated from the experimenters, which eliminated any possibility of clinical evaluation. In the final analysis, categories 2 and 3 were combined into one, and a "bends" or "no bends" classification was used.

The possibility of systematic experimental bias due to inadequate gas mixing, position within the chamber, time of day of the exposure, or carbon dioxide level has been explored previously (Berghage et al. 1973; Berghage, Keating, and Woolley *in press*); none of these factors was found to have a significant influence on experimental outcome. To avoid the possibility of observer bias, the experimenter did not make any of the observations himself; a technician who had no knowledge of the anticipated experimental outcome was trained to serve as the observer throughout the study.

RESULTS

Table 1 presents the basic features of the experimental design and a summary of the raw-data results. If we deal only with the data obtained during the 7-ATA exposures, there are three independent variables (exposure time, inert gas combinations, and animal weight) and two dependent variables (time of onset of symptoms and the incidence of decompression sickness). Table 2 presents intercorrelations for evaluating the independence of these variables. Several interesting relationships are shown in Table 2; some of these were expected and some were not. Exposure time was related to both of the dependent variables, as would be expected. The longer the exposure, the higher the incidence of decompression sickness and the shorter the interval between decompression and the manifestation of symptoms.

The high correlation between exposure time and animal weight is a disturbing relationship that tends to confound the experimental results. Animal weight is a nuisance variable in this study, and we had intended to control it experimentally by only using animals weighing between 200 and 300 g. Because of the apparent failure of the experimental control, we had to handle the effect of weight statistically, using the partial correlation. The values in parentheses in Table 2 are intercorrelations with the effects of animal weight partialed out. The high correlation (r = 0.51) between animal weight and the incidence of bends is reduced to a nonsignificant relationship (r = 0.23) if the effects of exposure time are partialed out statistically. The only relationships that hold up throughout all statistical manipulations are the ones between exposure time and bends incidence, between helium concentration and interval to symptom onset, and between interval to symptom onset and bends incidence.

A graphic display of the incidence of decompression sickness for a 7-ATA exposure involving various combinations of inert gas and time is shown in Fig. 1. If the incidence of decompression sickness is to be minimized, it appears that the composition of the diluent gas must be altered according to the length of exposure. The longer the exposure, the more helium required.

TABLE 2
INTERCORRELATION MATRIX FOR INDEPENDENT AND DEPENDENT EXPERIMENTAL VARIABLES FOR 7-ATA EXPOSURES

Variables	1	2	3	4	5
1. Exposure time	–				
2. Animal weight	0.51	–			
3. Helium percentage	0.00	0.14			
4. Time of onset	(−0.31)	−0.18	(−0.35)		
5. Incidence	(0.65)	0.51	(−0.04)	(−0.62)	–

[r = 0.33] = [P < 0.05]; [r = 0.44] = [P < 0.01]. Numbers in parentheses are partial correlations removing effects of animal weight from the relationship. Values were calculated using the formula:

$$r_{12.3} = \frac{r_{12} - r_{13}\, r_{23}}{\sqrt{(1 - r_{13}^2)(1 - r_{23}^2)}}$$

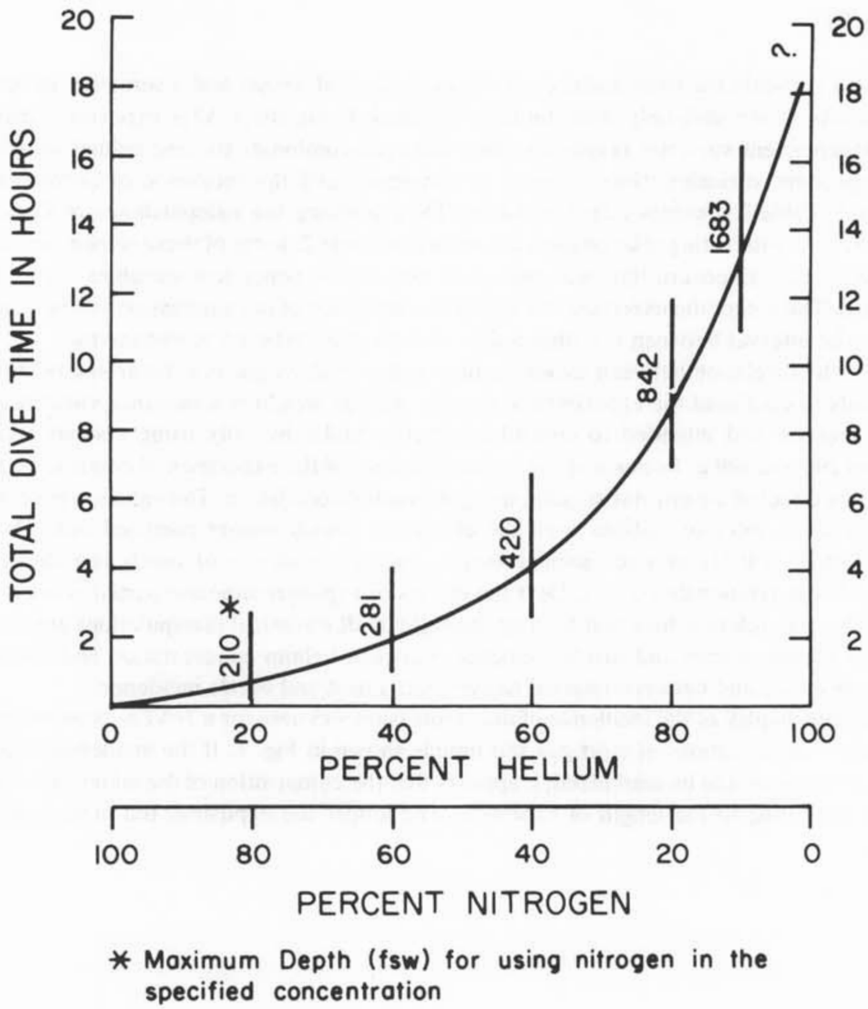

Fig. 1. Incidence of decompression sickness for an abrupt reduction in pressure after an exposure to 7 ATA with various times and inert gas combinations. Each data point is based upon 20 rats.

Results obtained for the 16.2-ATA exposures (Table 1) are not nearly as complete as those for the 7-ATA exposures, but the same general relationship seems to exist: the optimal inert gas combination shifts with exposure time. The longer the exposure, the more helium is needed in the diluent gas. The difference between the optimal combinations of inert gas for various times at 7 ATA and 16.2 ATA is probably the result of the additional 5 min of pressure at 16.2 ATA necessitated by the longer compression time.

DISCUSSION

Results of this study support the hypothesis that there is a potential decompression advantage in the use of multiple inert gases. The exact relationship between gas-uptake times for helium and nitrogen and the observed decompression results is still undetermined. The idea suggested by Webster (1955) that the decompression requirement is based upon the simple sum of the inert gas partial pressures does not appear to be true for our study. Webster concluded that the uptake characteristics of the individual inert gases would govern the total volume of gas present and would therefore alter the decompression requirement. This may be true, but the relationship between time and the uptake of multiple inert gases is not a simple additive one.

Figure 2 displays the empirically derived gas-uptake curves for rats for both helium-oxygen and nitrogen-oxygen. These curves were obtained by compressing rats to 7 ATA at the rate of 1.82 atm/min, maintaining them at 7 ATA for a selected period of time, and then abruptly (in approximately 20 s) decompressing them to the surface. The rats were considered to have reached equilibrium at 7 ATA when the incidence of decompression sickness stabilized. Based upon these curves, it appears that the half times for helium and nitrogen are approximately 8 and 23 min, respectively. Several attempts to apply the Haldane gas exchange model to explain the Fig. 1 data have produced negative results. It appears obvious that the use of multiple inert gases can provide some decompression advantage, but the explanation for the advantage still eludes us.

An oxygen diluent consisting primarily of an inert gas with high molecular weight provides an advantage for short-duration exposures. As exposure time increases, however, a greater proportion of the oxygen diluent should be a low molecular-weight gas. In current diving practice, this probably means using nitrogen, helium, or perhaps neon. Neon has a molecular weight just slightly less than that of nitrogen and somewhat greater than helium.

If this generalization about the importance of molecular weight is valid, the speed with which a neon mixture saturates a tissue should be between those of nitrogen and helium. Bennett and Hayward (1968) reported a study using crude neon (25% helium and 75% neon) in which the relative advantage of neon could not be determined because of the helium in the mixture. They suggested that a neon-helium-oxygen mixture might be one of the best mixtures for use in deep diving. Our results indicate that the truth of this assumption would depend upon the total time required for the dive.

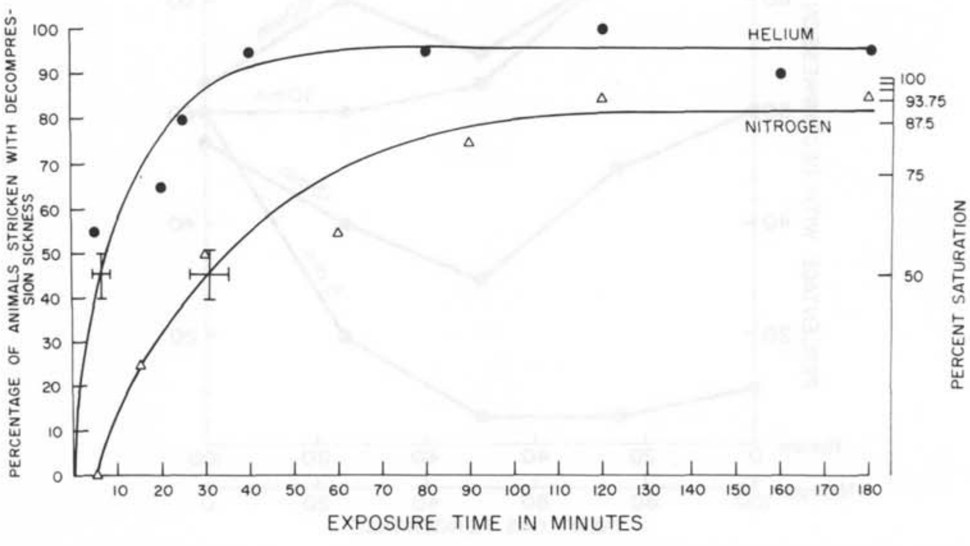

Fig. 2. Incidence of decompression sickness for rats exposed to 7 ATA breathing helium-oxygen or nitrogen-oxygen for various periods of time.

Results of our study relate to single, abrupt pressure reductions; whether they pertain to a more complex multistage decompression or to a continuous ascent has yet to be determined. As suggested in the RESULTS section, the relationship between time and optimal inert gas mixture appears to be independent of the pressure level. Admittedly, data from the 16.2-ATA exposures are far from conclusive. But if one adds the additional compression time to the time spent at 16.2 ATA, the optimal gas combinations come very close to those that might be expected based upon the 7-ATA results.

To extrapolate from our experimental results on the relationship between total exposure time and the optimal combination of helium and nitrogen to human diving is hazardous at best. We feel a certain obligation, however, to interpret our experimental results in terms of general principles and to speculate on the impact of these principles for human diving. In Fig. 3, we have related saturation time and optimal gas mixture for a rat to saturation time for man.

The assumption necessary for such an extrapolation is that the shapes of the relationship between time (degree of saturation) and inert gas combination are the same for all organisms. If one accepts this, (and there is some evidence to support it (Berghage, David, and Dyson *in press*), one needs only to determine the nitrogen saturation time for man. Estimates of this value range from 8 to 24 h; for purposes of this extrapolation, we used 20 h as a conservative estimate. This assumption will certainly have to be tested on larger animals and men before it can be accepted. Nevertheless, based upon these experimental results one may speculate that there is an optimal inert gas mixture for any given dive duration. The possibility that there may be an optimal or ideal gas mixture for each dive should probably be pursued and expanded to include more than two inert gases (Bond, Fishback, Lippitt, and Woodson *in press*). It is also possible that the oxygen partial pressure itself is dependent upon the time/pressure profile of the dive (Berghage et al. 1973).

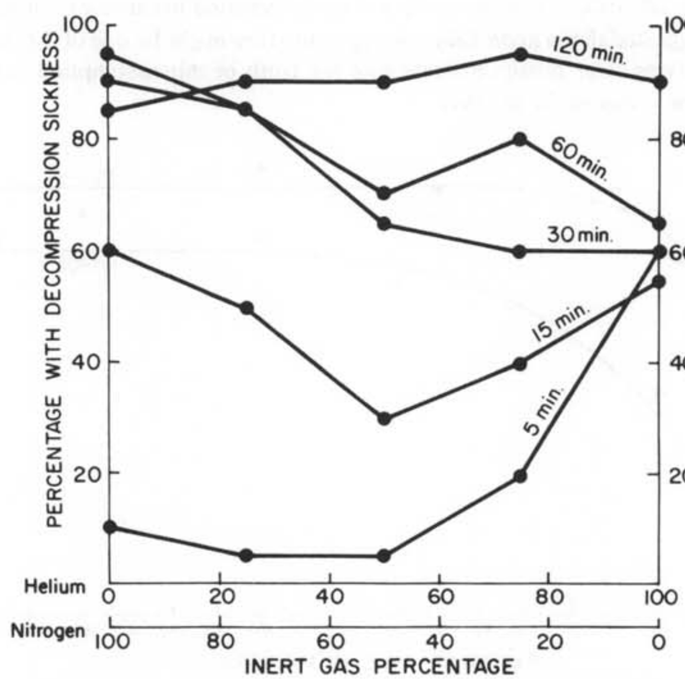

Fig. 3. Theoretical curve for determining optimal inert gas combination for human dives of various durations.

Experimental results of this study suggest some possibilities for future diving research. If these results are confirmed and there is a desire to use optimal gas mixtures, engineers will be required to develop new gas-mixing techniques for altering the gas mixture for each dive. Hardware already exists (the Mix Maker[1]), and this idea should therefore be relatively easy to implement.

Naval Medical Research and Development Command, Research Task M0099-PN.01-1190. The opinions and statements contained herein are the private ones of the writers and are not to be construed as official or reflecting the views of the Navy Department or the naval service at large.

The experiments reported herein were conducted according to the principles set forth in the "Guide for the Care and Use of Laboratory Animals," Institute of Laboratory Animal Resources, National Research Council, DHEW, Pub. No. (NIH) 74-24.

The authors thank Mary M. Matzen and Doris N. Auer for their help in the preparation of this paper.—*Manuscript received for publication June 1977; revision received December 1977.*

Berghage, T. E., C. Donelson, IV, and J. A. Gomez. 1978. Avantages du trimix (mélange gazeux triple) pendant la décompression. Undersea Biomed. Res. 5(3):233–242.—L'expérimentation animale a montré que, pour des expositions hyperbares à saturation, les mélanges de gaz inertes multiples ne protègent pas mieux contre la maladie de décompression que les mélanges hélium-oxygène. On a suggéré, cependant, que les différences entre l'azote et l'hélium en ce qui concerne l'échange gazeux pourraient fournir un avantage pendant la décompression des plongées brèves, si les mélanges comportaient les proportions qu'il fallait. Pour évaluer cette possibilité, nous avons soumis 700 rats albinos à 2 pressions (7 et 16,2 ATA), à 5 durées d'exposition (5, 15, 30, 60, et 120 min), et à 5 combinaisons de gaz inertes (hélium/azote: 0/100, 25/75, 50/50, 75/25, et 100/0). La pression partielle de l'oxygène a été maintenue à 0,51 ATA. Pendant chaque exposition les 5 rats ont exercé dans une cage rotative. Après l'exposition hyperbare, les animaux ont subi une décompression rapide à une pression plus basse (1 ou 4,9 ATA, selon la pression d'exposition) pour une demi-heure d'observations. Au cours de laquelle la pression partielle de l'oxygène a été maintenue à 0,2 ATA. L'incidence de bends notée à la fin de cette période constitue le variable dépendent. Les résultats de ces expériences nous font penser que l'utilisation de combinaisons de gaz inertes multiples puisse faciliter la décompression à la suite de plongées de courte durée. La combinaison optimale de gaz inertes dépend de la durée de l'exposition ($P<0{,}005$): il faut augmenter la concentration relative de l'hélium au fur et à mesure que se prolonge la durée de l'exposition.

mélange gazeux triple
maladie de décompression
optimisation de la décompression

REFERENCES

Bennett, P. B., and A. J. Hayward. 1968. Relative decompression sickness hazard in rats of neon and other inert gases. Aerosp. Med. 39: 301–302.

Berghage, T. E., K. J. Conda, and F. W. Armstrong. 1973. The synergistic effect of pressure and oxygen and its relationship to decompression sickness in mice. Joint Technical Report, U.S. Naval Medical Research Institute, Bethesda, Md., and the Navy Experimental Diving Unit, Washington, D.C.

Berghage, T. E., T. D. David, and C. V. Dyson. (*in press*) Species differences in decompression. Undersea Biomed. Res.

Berghage, T. E., L. J. Keating, and J. M. Woolley. (*in press*) Decompression sickness in rats and mice rapidly decompressed after breathing various concentrations of carbon dioxide. Pages 485–496, *in* C. W. Shilling and M. W. Beckett, Eds. Underwater physiology VI. Proceedings of the sixth symposium on underwater physiology. Federation of American Societies for Experimental Biology, Bethesda, Md.

[1]Gas-blending apparatus for hyperbaric use, manufactured by Airco Cryogenics, a division of Air Reduction Co. Inc., 1900 Main St., Irvine, CA 92664.

Bond, G. F., F. L. Fishback, M. W. Lippitt, and R. D. Woodson. (*in press*) Multiple inert gas transport patterns. Pages 335–342, *in* C. W. Shilling and M. W. Beckett, Eds. Underwater physiology VI. Proceedings of the sixth symposium on underwater physiology. Federation of American Societies for Experimental Biology, Bethesda, Md.

Keller, H., and A. A. Bühlmann. 1965. Deep diving and short decompression by breathing mixed gases. J. Appl. Physiol. 20(6): 1267–1270.

Momsen, C. B. 1942. Report on the use of helium-oxygen mixtures for diving. U.S. Navy Experimental Diving Unit, Washington, D.C.

Sayers, R. R., and W. P. Yont. 1926. The value of helium-oxygen atmosphere in diving and caisson operations. Anesth. Analg. 5: 127–138.

Webster, A. P. 1955. Some theoretical aspects of the use of multiple-gas mixtures for deep-sea diving. *In* L. G. Goff, Ed. Proceedings of the underwater physiology symposium, National Academy of Sciences, National Research Council Publ. 377, Washington, D.C.

Wex, T. G., D. G. Long, and E. T. Flynn. 1971. Incidence of decompression sickness in mice as a function of the relative concentrations of helium and nitrogen in the inspired gas mixture. Report 11–71, U.S. Navy Experimental Diving Unit, Washington, D.C.

Workman, R. D. 1963. Studies of decompression and inert gas-oxygen mixtures in the U.S. Navy. *In* Proceedings of the second symposium on underwater physiology. National Academy of Sciences, National Research Council Publ. 1181, Washington, D.C.