Role of oxygen in the production of human decompression sickness

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WEATHERSBY, P. K., B. L. HART, E. T. FLYNN, AND W. F. WALKER. *Role of oxygen in the production of human decompression sickness.* J Appl. Physiol. 63(6): 2380–2387, 1987.—In the calculation of decompression schedules, it is commonly assumed that only the inert gas needs to be considered; all inspired O_2 is ignored. Animal experiments have shown that high O_2 can increase risk of serious decompression sickness (DCS). A trial was performed to assess the relative risks of O_2 and N_2 in human no-decompression dives. Controlled dives (477) of 30- to 240-min duration were performed with subjects breathing mixtures with low (0.21–0.38 ATA) or high (1.0–1.5 ATA) P_{O_2}. Depths were chosen by a sequential dose-response format. Only 11 cases of DCS and 18 cases of marginal symptoms were recorded despite exceeding the presently accepted no-decompression limits by >20%. Analysis by maximum likelihood showed a shallow dose-response curve for increasing depth. O_2 was estimated to have zero influence on DCS risk, although data variability still allows a slight chance that O_2 could be 40% as effective as N_2 in producing a risk of DCS. Consideration of only inert gases is thus justified in calculating human decompression tables.

diving; mathematical modeling, human trial; sequential trial; nitrogen; dose-response; hyperbaric medicine

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HUMAN DECOMPRESSION SICKNESS (DCS) results from a series of mechanisms sufficiently unknown as to prevent effective prediction of its occurrence. "Safe decompression" procedures are calculated by various means, but a final testing phase is always required. Typically the first calculations produce an unsafe set of procedures, and revision and retesting is the historic norm. Any information to increase the accuracy of prediction would save people and resources.

To calculate an acceptable decompression, numerous assumptions are made. With a single recent exception (21), a standard assumption is that only the inert gas needs to be considered in decompression calculations. All inspired O_2 is ignored. A frequent application of this assumption is the equivalent air depth (EAD) calculation in which a dive on any N_2-O_2 mixture is considered to be equivalent for decompression purposes to an air dive with the same inspired N_2 partial pressure (7). This assumption may be correct. Alternatively, it may be incorrect and unsafe, because there is no physical or chemical reason why O_2 cannot be a component of a bubble in tissue (9). By this mechanism, any extra levels of O_2 in whatever tissue is at risk would add to the bubble volume and thus to the dose of bubbles. (Decompression decisions are made on tissue gas tensions at the moment of decompression but the history of bubble evolution would certainly be affected by gases breathed subsequently.) On the other hand, the assumption may be incorrect but safe because O_2 decreases the blood flow, and thus the rate of inert gas uptake, in at least some tissue beds. The local flow control of O_2 is well described in many tissues, including skeletal muscles (4), but may not operate in other tissues (13) or under hyperoxic conditions Even more complex O_2 effects may occur in possibly relevant spaces such as synovium (19). This O_2 regulatory mechanism would reduce the total amount of N_2 delivered to a diver's tissues and thus decrease his total inert gas content. Neither line of reasoning can be pursued much further because the actual composition (and in fact the occurrence) of bubbles is unknown as are the identification and characteristics of the tissue beds responsible for DCS. The latter makes estimates of actual tissue P_{O_2} during diving nearly impossible.

Some experimental approaches to address the assumption of no-O_2 effect have been reported. Donald (6) demonstrated that goats can suffer a form of DCS when extra O_2 is breathed, and subsequent quantitative studies in both goats (8) and rats (18) concluded that one-fourth to one-third of the inspired O_2 should be added to the estimated N_2 partial pressure in assessing total DCS risk. Berghage and McCracken's (2, 3) more recent rat studies demonstrated an O_2 contribution to DCS, but the results needed allowance for direct O_2 solubility and oxyhemoglobin binding (26) to have a consistent interpretation. Very recent work, also in rats, estimates O_2 as 40–80% as potent in causing near-fatal DCS as is N_2 (R. S. Lillo, unpublished observations). However, as with the previous animal work, O_2 was used in such high concentrations that the risk of O_2 toxicity would preclude similar exposures to humans. The only direct study with humans appeared to show a slight contribution of O_2 but was terminated short of statistically significant results (16). A recent failure of extrapolation from air to mixed N_2-O_2 decompression tables in a test series of human decompression tables (20) has led to a decompression calculation that assumes a DCS risk due to O_2 (21).

This report describes a trial of 477 human exposures intended to establish the magnitude of any O_2 contribution to DCS risk under conditions of N_2-O_2 diving with immediate return to the surface (no-decompression dives). The trial was sequential in design, with the diving depths established by recent history of the trial rather

than in advance. The raw data were in the form of DCS dose-response observations that could be analyzed by appropriate models using maximum-likelihood estimation (14, 24). Dose in this context is the diving depth, or more generally the depth-time combination, which is directly tied to the incidence of DCS. Statistical models of DCS incidence depend on dose-response formulations, and this trial was expected to provide an excellent opportunity to estimate the shape of the dose-response function.

METHODS

Experimental design. The experiment was intended to simulate operational diving in conditions of water immersion, cold, exercise, and breathing gear but to closely control gas composition, depth, and time. Dives were divided into six series that specified a bottom time (30, 60, and 240 min) and a gas mixture (high or low O_2) (Table 1). The starting depth for each series was chosen to be ~8% shallower and presumably safer than the US Navy Diving Manual no-decompression limits on compressed air (22) when the assumption of no-O_2 influence is applied. The entry of EAD in Table 1 gives the depth equivalent for the same N_2 partial pressure with compressed air. For example, the *series 1* gas mixture at 66 ft has the same N_2 partial pressure as air at a depth of 80 ft of seawater (fsw). The US Navy no-decompression air limits are 90 fsw for 30 min, 60 fsw for 60 min, and 35 fsw for 310 min. The O_2 fraction was selected to maintain at least normoxia ($Po_2 > 0.21$ ATA) for *series 1, 3,* and *5* and to be below substantial risk of O_2 toxicity (Po_2 1.3–1.5 ATA) for *series 2, 4,* and *6.*

Rules for pressure change within each series were as follows. *1*) With no DCS cases in 10 exposures at this pressure, add 4% in pressure. *2*) With 1 DCS case in 20 exposures at this pressure, add 4% in pressure. *3*) With 2 DCS cases in any number of exposures, or 1 serious case, subtract 2% in pressure. Each subject was limited to two exposures in each series for a total of up to 12 exposures. This limitation was a compromise between studying a few people extensively and trying to get a very large population to have a few exposures each. In the only large controlled population study of decompression, Gray et al. (11) found that DCS tended to be more random than reproducible in the same individual. The order of dives (i.e., which series next) followed a table of random numbers but was constrained (stratified) to achieve equal numbers of exposures in each series at multiples of 72 exposures.

TABLE 1. *Experimental conditions*

Series	Bottom Time, min	O_2, %	Depth, fsw	EAD, fsw	Po_2, ATA
1	30	10	66–91	80–108	0.30–0.38
2	30	30	95–130	80–111	1.16–1.48
3	60	10	43–59	53–72	0.23–0.28
4	60	35	72–96	53–73	1.11–1.37
5	240	12	25–38	32–46	0.21–0.26
6	240	40	50–74	30–48	1.01–1.30

EAD, equivalent air depth.

Subjects. A total of 61 active duty US Navy divers volunteered after the study was approved by the local Committee for the Protection of Human Subjects. With three exceptions, all were stationed at this Institute. Subjects participated in 1–12 successful exposures, with an average of eight exposures per subject. Physical attributes of the subjects have been detailed in another report (23). Volunteers for the trial were solicited from all male divers under age 40 yr. Prospective subjects were briefed singly and in groups on the purpose and design of the study before informed consent was elicited. Approximately 85% of those who were eligible eventually volunteered. For acceptance as a subject, no chronic or acute medical condition that would cloud the diagnosis of DCS was allowed. No other blanket disqualifications were instituted to approach a representative sample of the total Navy diving population. Medical problems noted in subjects accepted into the study included: gas pockets in the pelvis (12), recent arthroscopic knee surgery, twice ruptured tympanic membrane, history of fracture with internal fixation, and history of low back pain. These conditions did not result in permanent disqualification from routine Navy diving and in fact none of these problems recurred after any experimental dive.

Qualification standards for a particular scheduled dive were more severe. To avoid mistaking muscle strain with DCS, a subject was temporarily excused if he had participated in physical exercise on the scheduled day unless it was much less than his normal regimen. He was also excused if he had taken any systemic drug other than antibiotics. Aspirin and oral decongestants were not permitted. Divers were also excused for respiratory illnesses with significant sinus or joint involvement, less than average sleep the night before, or consumption of over 2 oz of alcohol during the preceding 24 h. No diver was scheduled if he had been exposed to increased atmospheric pressure for any reason in the preceding 7 days. This last requirement was an effort to avoid an acclimatization effect that is demonstrable in some pressure exposures (10) and suspected in others (21).

If a diver suffered DCS, he was disqualified for 2 wk in cases of simple pain-only symptoms and 4 wk after more serious cases. Only one subject declined to reenter the trial after suffering DCS.

Equipment. A large pressure chamber with a suspended wet pot was used for all exposures. Water was kept between 69 and 72°F, except for the long dives when a rise to 76°F was allowed for divers with significant susceptibility to cold. Divers were clothed in ¼-in. wet suits, but some used an additional partial wet suit if they expected to be very cold. A target of <1°C core temperature drop during the exposure was established. The low risk of severe hypothermia was insufficient to justify the discomfort of continuous temperature monitoring. However, all subjects in 4-h dives had a rectal temperature measurement immediately before and after the dive. Most measurements showed a drop of a few tenths of a degree, but more than 10 subjects actually had a temperature rise, and in 7 cases a drop of 1.0–1.5°C was found. All subjects used the US Navy Mk-1 divers mask for gas supply and communications (22). While at depth, sub-

jects exercised using a locally built sled ergometer (17) that allowed a standard work rate in a sitting position. The sled had spring-loaded pedals that were extended by the subject from a length of 28 to 44 in. (spring tension from 6.6 to 13.5 lbs) between two sets of magnetic switches. A timing light was placed near the subject to help him remain at 50 repetitions (each leg through a full extension-relaxation cycle)/min. The work was performed on a schedule of 5 min of work, 3 min of rest, with an additional 10 min of rest after each hour on the long dives. Overall the work cycle was very close to 50% of the total dive time. In preliminary measurements on two subjects, the exercise was found to produce an O_2 consumption of 1–1.5 l/min.

Gas mixtures were prepared from pure O_2 and N_2. Mixtures were made in large batches (60–180 cu ft at 4,000 psig), and the analysis of each batch fell within 0.2% O_2 of the target value by both paramagnetic O_2 analysis and mass spectrometry. Composition of the breathing gas was also verified before and during each dive with a paramagnetic O_2 analyzer.

Procedure After equipment check-out, subjects descended 9 ft into a water-filled chamber while breathing compressed air from the Mk-1 emergency gas supply. Then the chamber above was compressed with air at a specified rate of 75 fsw/min. Compression was stopped for 10 s at 30 ft of seawater gauge pressure (fswg) for breathing gas to be switched to the experimental mixture, then compression resumed. If subjects had difficulty in equalizing pressure in ears or sinuses, compression was slowed or reversed. Actual total descent times for each dive are tabulated elsewhere (23). If the final pressure could not be reached within 2 min of the scheduled descent time (or 1 min in the case of 30-min dives), the dive was aborted. Dive bottom time was defined as the interval from subject leaving the water surface until the start of decompression. Time at depth was spent in the exercise described above.

Control of depth was tight. Depth was defined as the air pressure in the chamber above the wet pot plus the water depth at midchest level on the diver. A high-precision differential digital pressure gauge (Mensor, San Marcos, TX, serial 2237 with overall accuracy specification of 0.04% of full scale or 0.2 fsw) was used to control depth via manually operated supply and exhaust valves. Daily variations in ambient barometric pressure on the reference side of the gauge were ignored. A pen plotter was attached to the gauge auxiliary output and monitored through the dive. Deviation of 1 fsw for 30 s, or any other combination of pressure excursions adding up to that value, was reason to abort the dive. Decompression was accomplished by manual control of exhaust. At the end of the dive (30, 60, or 240 min after the divers first left the surface), a large valve was opened for a target ascent rate of 60 ft/min. Actual rates were within 10% of the target rate except for shallow depths. Travel from 10 ft to the surface took 18–20 s, as measured on a separate recorder used on every dive. Again, a 10-s hold at 30 fsw was used to switch the diver's gas back to compressed air. The *series 5* dives, being shallow, had the change of gas occur at the full dive depth; otherwise the procedures were identical.

After leaving the chamber, the divers were interviewed briefly by a physician experienced in hyperbaric medicine and examined in more detail 2 h after the dive. Subjects were strongly encouraged to report all symptoms of any kind for 18 h and were generally interviewed by a physician the following morning.

RESULTS

Symptoms. A total of 477 exposures were completed according to all specifications. Another 47 exposures were aborted during the dive for violation of the protocol. The most frequent reason for aborts was inability of a diver to equalize pressure in his ears fast enough to arrive at bottom depth within the short allowable time. Less common were equipment malfunctions and failure to maintain the required depth. A chronological record of all successful dives is available (23).

Diagnostic outcome did not fall into the clean categories of DCS or no DCS. The spectrum of symptoms was forced into final categories of definite DCS, no DCS, and marginal symptoms. Some 54 exposures were followed by a report of symptoms of one kind or another. Of the 54 incidents, 13 cases had persistent symptoms that were provisionally diagnosed as DCS by a physician and were treated on a US Navy hyperbaric O_2 treatment table. Most symptoms were rather mild and gradual in onset, and relief was prompt with recompression. No subject had any measurable or subjective symptom persisting for as long as 1 wk after the dive. Four of the treated cases had no prompt relief of the ambiguous presenting symptom and were concluded on that basis to not represent DCS. Two of the unresponding cases were treated within 4 h of the dive and were then considered as being interrupted postdive observation and were therefore not included with the 477 exposures as final data. The rationale is that the unwarranted treatment masked any actual DCS that might have occurred later. The other two unresponsive cases were treated 18-20 h postdive and were declared to be acceptable uneventful exposures.

On a review of records after the entire experiment, a diagnosis of DCS was made in an additional three cases based on the symptoms reported orally more than a day after a dive but not treated with recompression. At the time of the review, another 18 cases were declared as having marginal decompression symptoms (frequently called "niggles") that did not warrant treatment. This category was defined as mild joint pain or discomfort that lasted for 2–60 min, or for a shorter period but on more than one occasion that day, or occurred in more than one site. These cases were not treated since the symptoms did not persist for long enough to better evaluate or to observe a possible improvement with treatment. The marginal cases also include five cases of simple "skin bends" that presented as a mottled rash on the trunk.

The symptoms of the DCS and marginal cases are listed briefly in Table 2 and in more detail elsewhere (23). A large number of anatomic sites were involved in

TABLE 2. *DCS incidents*

Case No.	Series	Depth	Diagnosis	Onset Time		Site
				No symptoms	Definite symptoms	
1	*6*	50	D	+ 2 h	+ 6 h	Back, skin
2	*4*	72	M	+ 2 h	+ 4 h	Skin
3	*3*	46	D	+ 4 h	+ 12 h	Legs
5	*2*	105	M	+ 1 h	+ 2 h	Skin, shoulder
6	*3*	46	D	+ 1 h	+ 105 min	Forearm, hand
8	*1*	71	D	+ 2 h	+ 4 h	Upper arm
9	*1*	71	M	+ 1 h	+ 2 h	Forearm
10	*1*	71	M	+ 2 h	+ 6 h	Shoulder, elbow
12	*4*	80	M	+ 5 min	+ 20 min	Knee, heel
13	*5*	29	D	+ 2 h	+ 7 h	Shoulders
16	*4*	80	M	+ 2 h	+ 6 h	Elbow
17	*1*	75	M	+ 5 min	+ 1 h	Knee, shoulder, elbow
19	*6*	58	M	+ 1 h	+ 2 h	Skin, cardiovascular
20	*5*	33	D	+ 2 h	+ 6 h	Shoulder
21	*4*	88	D	+ 2 h	+ 3 h	Shoulder
28	*4*	88	M	+ 5 min	+ 20 min	Ankle, knee, jaw
29	*5*	35	M	+ 5 min	+ 1 h	Hip, ankle, shoulder
32	*5*	35	D	+ 5 min	+ 1 h	Neck, shoulder, wrist
33	*5*	34	M	+ 1 h	+ 2 h	Shoulder, foot
36	*5*	34	M	+ 5 min	+ 2 h	Shoulder
37	*3*	56	M	+ 2 h	+ 6 h	Shoulder
38	*2*	125	D	+ 2 h	+ 4 h	Shoulder, wrist, elbow
39	*6*	70	M	+ 1 h	+ 2 h	Shoulder
42	*3*	59	M	+ 1 h	+ 2 h	Skin
48	*4*	96	D	+ 5 min	+ 20 min	Eye
49	*6*	74	M	+ 2 h	+ 6 h	Wrist, arm
51	*5*	36	M	+ 1 h	+ 2.5 h	Knee
52	*2*	130	D	+ 0	+ 4 min	Hip
53	*6*	74	M	+ 2 h	+ 3.5 h	Skin, abdomen

DCS, decompression sickness; D, confirmed DCS; M, marginal symptoms as described in text.

symptom presentation. Most cases had a subjective feature of pain, and a majority were accompanied by a slight sensory or motor loss. Symptoms onset was usually gradual. The times at which the subject last had no symptom and the time the symptom was definite are also listed A striking feature of the time of symptom presentation is the significant time lag (frequently several hours) between dive and symptom.

A summary of outcome by exposure condition is presented in Table 3. Most series covered a 30% span in absolute pressure. The data within each series are striking in their variability; no clear increase in DCS incidence with exposure depth is evident. That observation clearly contradicts the common view that a threshold exists beyond which safe diving suddenly becomes hazardous. The variability is also evident across series: no O_2 or time grouping has a predominance of the symptoms.

Variability was evident in the response of individuals as well. No subject had DCS twice with the same exposure. In the four instances where subjects had two dives in a series, one of which resulted in DCS, the other dive was uneventful. In three of the four cases, the other exposure was to the same or greater depth as the problem dive. There was no statistically significant association between symptoms and the age, weight, or body fat of the subjects (23).

Analysis. Questions about the shape of the decompression dose-response function and the effect of O_2 need to be addressed by analysis.

Even from inspection of the raw data in Table 3, the dose-response function is not very steep, i.e., a few feet deeper in the dive depth (the dose) does not convert a very safe dive to one that is very hazardous. One indication of how "softly" the DCS risk increased with depth in this study is an overall comparison of dives to the current US Navy no-decompression limits using the EAD assumption. Dives allowed by present rules had 2.1% DCS and 5.4% DCS + marginals of 186 exposures. On the 291 dives beyond the limit, there was a 2.4% incidence of DCS and 6.5% rate of DCS + marginals. The limits clearly do not separate regions of greatly different DCS risk.

To define better the dose-response and O_2 effect a specific probabilistic model is needed (24). In the present case, the model needs to use depth, time, and O_2 content to predict the probability of decompression sickness, P(DCS). First, we define a risk model

$$P(\text{DCS}) = 1.0 - \exp(-\text{R}) \qquad (1)$$

where R is the decompression risk that results from a particular depth, time, and gas mixture. Note that a small value of R leads to only a small chance of DCS, whereas a large value of R makes the probability of bends approach 1.0 (i.e., 100%). In principle R could also include measures of individual susceptibility (e.g., percent body fat) were such measures available. For now we use only the following expression where R is formulated with a "tissue supersaturation"

$$\text{R} = [k1(P_{N_2} + k_{O_2} * P_{O_2} - 1\text{ATA})]^n \qquad (2)$$

TABLE 3. *Summary of outcome*

Bottom Time, min	Depth, ft	Dives	DCS	Marginal	Depth, ft	Dives	DCS	Marginal
30	*Series 1 (10% O_2)*				*Series 2 (30% O_2)*			
	66	2	0	0	95	10	0	0
	67	10	0	0	100	10	0	0
	71	21	1	2	105	10	0	1
	75	9	0	1	110	10	0	0
	79	10	0	0	115	10	0	0
	83	11	0	0	120	10	0	0
	87	10	0	0	125	11	1	0
	91	3	0	0	130	7	1	0
60	*Series 3 (10% O_2)*				*Series 4 (35% O_2)*			
	43	10	0	0	72	12	0	1
	44	10	0	0	76	10	0	0
	46	10	2	0	80	10	0	2
	47	11	0	0	84	10	0	0
	50	10	0	0	88	19	1	1
	53	10	0	0	92	9	0	0
	56	10	0	1	96	12	1	0
	59	8	0	1				
240	*Series 5 (12% O_2)*				*Series 6 (40% O_2)*			
	25	10	0	0	50	20	1	0
	27	10	0	0	54	10	0	0
	29	10	1	0	58	10	0	1
	31	10	0	0	62	10	0	0
	33	11	1	0	66	10	0	0
	34	10	0	2	70	10	0	1
	35	7	1	1	74	11	0	2
	36	11	0	1				
	38	2	0	0				
	Total	477	11	18				

DCS, decompression sickness.

where P_{N_2} and P_{O_2} are computed N_2 and O_2 partial pressures in tissue immediately before decompression, which when decreased by the postdecompression ambient pressure of 1 ATA represent the calculated gas supersaturation This calculation refers to the time of decompression itself and ignores the tissue gas tensions later as they return to normal atmospheric steady state. The parameter k_{O_2} allows for O_2 to have less (or more) of an impact on risk compared with N_2; parameter n allows for greater or lesser steepness of the dose-response curve compared with a simple exponential (with large n's producing steeper sigmoid curves); and parameter $k1$ has units of ATA^{-1} to establish the pressure-probability scale conversion. If the calculated R in *Eq. 2* is negative, we set it at zero to avoid negative risks.

It is still necessary to calculate the tissue tensions of N_2 and O_2. O_2 is assumed to achieve a tissue steady-state value very quickly in comparison to the experimental time (30 min or more). Levels of O_2 in tissue are subject to different metabolic and solubility effects than N_2. O_2 is substantially lower than the inspired P_{O_2} in tissue. Measurements of tissue P_{O_2} under hyperoxia are rare, and no reliable calculations exist for tissues that may be involved in DCS, e.g., knee cartilage We chose to use inspired P_{O_2} in the analysis as a conservative measure since inspired P_{O_2} will actually exaggerate any O_2 effect. Attempts to include more complicated functions for O_2 were abandoned when the data seemed to provide no support for that complexity and mathematical problems during estimation increased. Tissue N_2 is slow enough to require a kinetic treatment, which as a first approximation is exponential in response to a change in ambient pressure.

$$P_{N_2} = 0.79 \text{ ATA} + [P_{I_{N_2}}(B) - 0.79][1.0 - \exp(-T/TC)] \quad (3)$$

Equation 3 states that some area of the body has been equilibrated with atmospheric N_2 (79% of 1 ATA) then increases during the dive bottom time (T) toward the bottom depth inspired N_2 pressure, $P_{I_{N_2}}(B)$, with a characteristic time constant (TC).

A modified model was also explored that allowed O_2 to exert its influence by changing the N_2 time constant

$$TC = TC0 + kTC(P_{O_2} - 0.21) \quad (4)$$

The parameter TC0 controls the kinetics during normoxia (P_{O_2} of 0.21 ATA) and kTC allows slower (positive kTC) or faster (negative kTC) N_2 uptake when breathing high O_2 gas.

The unknown parameters in *Eqs. 1–4* that must be estimated from the data are $k1$, k_{O_2}, n, and TC (or TC0 and kTC). The optimizing procedure of maximum likelihood was used to estimate these parameters. The likelihood function (14), which is the product over all dives of the probability of the event actually happening, is maximized. The probability is determined by the model, such as *Eqs. 1–4*, which relates details of the dive to P(DCS) if symptoms were observed or to P(no DCS) = 1.0 – P(DCS) if the dive was uneventful. Estimation was performed by a nonlinear least squares Marquardt algorithm modified for maximum likelihood as previously described (1, 24). The large number of marginal cases can have a significant impact on the data structure. As before (24), we have run parallel analyses on three possible interpretations of marginal cases: all considered as DCS, none considered as DCS, and each considered as one-half case.

Results of the parameter estimation from all 477 exposures are presented in Table 4 for the three diagnostic possibilities. Numbers in parentheses are approximate 1 SE uncertainties in estimated parameters. The column labeled LL gives the log likelihood, which can be used as a measure of goodness-of-fit. The LL increases when the model fits the data better.

For each set of entries in Table 4, the first entry is a null model that denies any effect of pressure or time and considers each dive to have equal chance of DCS. Here the only parameter is the (constant) probability of DCS. The maximum LL for this model can be considered a lower bound for more realistic models, but the manner in which DCS is spread across all conditions in Table 3 would lead us to expect that no model will do very much better. An improvement of ~2 LL units per additional parameter is needed to declare a significantly better fit to the data. The second entry in each section uses *Eqs. 1–3* with monoexponential gas exchange kinetics, no O_2 effect, and the dose-response exponent, n, fixed at 1.0. In each case, the fit to data is slightly better than the

TABLE 4. *Probabilistic model analysis of data*

Models and Parameters	LL
DCS cases only	
None – null model, P(DCS) = 0.02306	−52.338
TC = 74.7(57), kO_2 = 0.0F, n = 1.0F, $k1$ = 3.84(2.3) × 10^{-2}	−52.150
TC = 56.7(52), kO_2 = −0.1(0.3), n = 1.0F, $k1$ = 3.95(2.0) × 10^{-2}	−52.090
TC0 = 84.5(73), kO_2 = 0.0F, n = 1.0F, $k1$ = 3.63(2.2) × 10^{-2}	
kTC = −3.1(48)	−52.074
DCS cases + one-half marginal cases	
None – null model, P(DCS) = 0.0419	−83.010
TC = 88.5(54), kO_2 = 0.0F, n = 1.0F, $k1$ = 8.0(4.3) × 10^{-2}	−82.114
TC = 67.7(53), kO_2 = −0.09(0.25), n = 1.0F, $k1$ = 8.3(3.6) × 10^{-2}	−82.031
TC0 = 89.6(64), kO_2 = 0.0F, n = 1.0F, $k1$ = 7.9(4.2) × 10^{-3}	
kTC = −40(39)	−82.113
DCS + all marginal cases	
None – null model, P(DCS) = 0.0608	−109.306
TC = 94.0(40), kO_2 = 0.0F, n = 1.0F, $k1$ = 0.123(0.05)	−107.641
TC = 69.6(40), kO_2 = −0.09(0.17), n = 1.0F, $k1$ = 0.124(0.04)	−107.526
TC0 = 91.1(45), kO_2 = 0.0F, n = 1.0F, $k1$ = 0.122(0.05)	
kTC = 4.7(39)	−107.634

LL, log likelihood; DCS, decompression sickness; P(DCS), probability of DCS; TC, kO_2, n, $k1$, and kTC, parameters, see text. Entries with F indicate parameter fixed at that value and not estimated by data; entries in parentheses are 1 SE of the estimated parameter.

null model but not outside the improvement (increase in likelihood) that may occur simply by chance with the additional parameter The time constants for N_2 are in the range of 75–95 min.

Entries are not listed in Table 4 for the effect of varying exponent, n. It proved difficult by normal estimation procedures to deal with this parameter. However the allowable range covered 0.25–4.0 in all cases without achieving a statistically significant difference in maximum LL from the entries in Table 4. Thus the data under all diagnostic categories do not allow a precise estimate to be reached for this exponent. The exponent has its greatest effect in the middose range of the dose-response curve (near 50% DCS). In fact all curves with exponents between 0.25 and 4.0 have a similar shape in the <10% range exhibited in the data.

The final two entries in each section of Table 4 present the best estimates of how strongly O_2 affects DCS risk. The third uses the parameter kO_2 to compare O_2 and N_2 in providing a "gas dose" for DCS. If kO_2 = 1 then O_2 is fully as effective as N_2 in leading to DCS; if kO_2 = 0 then O_2 has no effect whatever; negative values of kO_2 mean that O_2 protects against some of the DCS risk due to N_2. In all cases the effect is small, i.e., the magnitude of kO_2 is much less that 1 and is actually quite close to 0. The 1 SE estimates of uncertainty in kO_2 are 0.2–0.3. An ~95% upper confidence limit on kO_2 can be set with 2 SE such that we can comfortably conclude that O_2 has <40% of the impact of N_2 in generating risk of DCS. Examination of the 95% confidence limits on kO_2 also allows rejection of the high values of kO_2 (~0.8) that would be consistent with recent animal decompression experiments (R. S. Lillo, unpublished observations).

The last entry in each section of Table 4 allows for O_2 to change the N_2 exchange kinetics. Positive values of kTC mean that O_2 increases the N_2 time constant, thus slowing N_2 uptake; negative values of kTC mean an accelerated uptake, and values of 0 mean no effect. Again very little effect is seen. The kTC's are small. Thus, in the first diagnostic group (DCS only), the N_2 time constant was estimated to decrease (faster exchange) by only 3 min per extra atmosphere of O_2. Again the large 1 SE parameter confidence limits show little precision in estimating an effect.

Model derived dose-response curves can be plotted such as in Fig. 1. The conditions are for an air (21% O_2) dive of 60-min duration. The parameters of Table 4 were used to plot the dose-response contours. The no-O_2 effect model (second entry in each diagnostic section of Table 4) was used for the depth range of 30–100 fsw. The experimental conditions of Table 1 show that EAD's for 1-h dives ranged from 53 to 73 fsw. The response curves all were gradual over the range of interest. Average predicted values of P(DCS) are quite close to the raw outcomes actually found for each diagnostic possibility. Also plotted in Fig. 1 is the maximally steep dose-response permitted by the data (n = 4) in *Eq. 2* with other

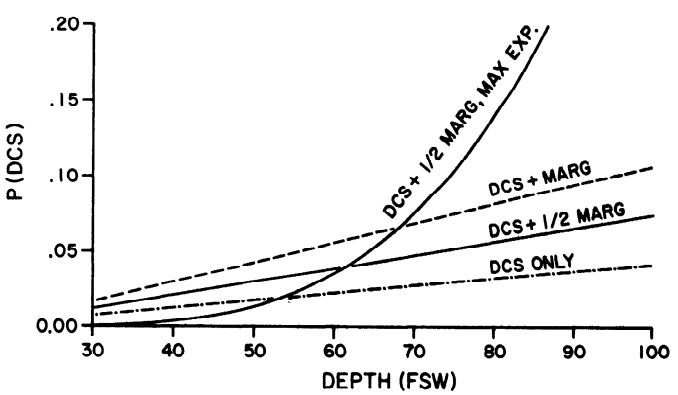

FIG. 1. Dose-response plot of calculated probability of decompression sickness [P(DCS)] against dive depth for a 1-h exposure breathing compressed air (21% O_2). Models used parameters of second entry in each diagnostic section of Table 4 (O_2 effect, exponent of 1.0). Additional *curve* uses maximum possible exponent (max exp) (n = 4.0) allowed by diagnostic category of DCS + ½ marginal (marg) cases. Current maximum allowed depth for these conditions is 60 ft (22).

parameters adjusted by maximum likelihood. The curve crosses the marginal = 0.5 case line in the range of the experiments and does not become very steep until deeper than the region for which we have data. No raw data is plotted in Fig. 1. Graphic presentations of these experiments are difficult (24). As with other binomial outcome experiments, the raw data would be plottable as a sequence of 0's (no DCS) or 1's (DCS). Plotting the raw percent incidence for each series-depth combination is also uniformative, since the binomial confidence limits are so huge. For example, a result of 0 cases in 10 dives has 95% confidence limits of 0–31% underlying incidence.

DISCUSSION

This study was intended to obtain quantitative answers on the effect of O_2 in human decompression sickness and on the strength of the DCS dose-response curve. The results support the traditional view of O_2 having no effect, but conclusions are limited by the variability of human DCS.

Some important numerical bounds can be established from the study. The dose-response function is flat: a 10% increase in depth appears to cause a <10% increase in risk of DCS. O_2 does not increase DCS to the same extent as N_2; O_2 is definitely <40% as potent and may actually exert a minor protective effect. O_2 is less potent in causing this mild degree of human DCS than it is in causing serious DCS in animals. Specifically, with a maximum safe O_2 level of ~1.2 ATA and a maximum O_2 effect of 40%, the greatest possible dose effect of O_2 would be $\sim(1.2 - 0.21) \times 0.4 = 0.4$ ATA or 13 fsw. The shallow dose-response indicates that a depth increase of <13 fsw would hardly affect the DCS incidence to an extent that could be noticed; certainly it would be within the noise of all but the largest conceivable study group.

Consideration of human decompression sickness as a population dose-response problem has a fairly recent origin (2, 3). Current decompression procedures are formulated as a boundary-avoidance problem, and the most common perception is that the imminence of DCS suddenly increases at this boundary. Animal experiments have shown the inapplicability of this view. With the application of probabilistic models to animal (15, 24) and human DCS (24), the need for proper dose-response formulations is more apparent. Human He-O_2 saturation-excursion diving was found to be fit quite well by several different response curves (24), whereas animal response data are more extensive and therefore have much better-defined shapes. The responses in Fig. 1 are quite gradual; if a sharp boundary exists, it lies with more severe dives that would present ethical problems for a direct human study. The possibility of extrapolating the curve shape from rats to humans would need a serious quantitative examination before acceptance as reasonable basis to protect human safety.

A major surprise in the study was the low overall incidence of DCS. A lengthy analysis of several thousand human air dives resulted in a model that appeared to provide an excellent ability to predict P(DCS) (25). When applied to the exposures listed in Table 3, a total of 23 DCS cases were predicted, mostly in the 240-min exposures The actual number is significantly lower. The discrepancy does not appear to be a simple difference in data type, nor does it appear to be a statistical fluke (23). Only if all the marginal cases were declared as DCS do the predictions and outcome start to agree. However we believe such a diagnostic grouping is not comparable to the older air diving data used to obtain the predictions (25). In reviewing old reports of DCS trials we were struck by the severity of symptoms required for a diagnosis of DCS. Not only would our marginal cases not have been scored as DCS by the prior investigators; many cases diagnosed and successfully treated in the present study would have been ignored. The only aspect of this trial that is clearly different from previous human work is the tight pressure control. Regardless of reason the low DCS incidence here makes conclusions difficult: inferences on any cause of DCS are weak if DCS is hardly ever caused.

The study was designed to provide a large data set to answer both questions of dose-response and O_2 effects The total study size was relatively large, and control of the experiments was unusually precise. Conditions of water immersion, temperature, breathing apparatus, and exercise were consciously chosen to simulate the operational and acceptance testing environments under which most information on human DCS has been obtained. Care was taken to minimize the human subjective element in both subject and observers. The pressure-time profiles were very carefully controlled. Discrepancies with previous human and animal work might possibly be due to exercise, immersion, pressure control, or some other factor. Specifically designed experiments would be required to examine each possibility.

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