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Modeling pulmonary and CNS O_2 toxicity and estimation of parameters for humans

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Arieli, R., A. Yalov, and A. Goldenshluger. Modeling pulmonary and CNS O_2 toxicity and estimation of parameters for humans. *J Appl Physiol* 92: 248–256, 2002; 10.1152/japplphysiol.00434.2001.—The power expression for cumulative oxygen toxicity and the exponential recovery were successfully applied to various features of oxygen toxicity. From the basic equation, we derived expressions for a protocol in which P_{O_2} changes with time. The parameters of the power equation were solved by using nonlinear regression for the reduction in vital capacity (ΔVC) in humans: $\%\Delta VC = 0.0082 \times t^2(P_{O_2}/101.3)^{4.57}$, where t is the time in hours and P_{O_2} is expressed in kPa. The recovery of lung volume is $\Delta VC_t = \Delta VC_e \times e^{-(-0.42 + 0.00379P_{O_2})t}$, where ΔVC_t is the value at time t of the recovery, ΔVC_e is the value at the end of the hyperoxic exposure, and P_{O_2} is the prerecovery oxygen pressure. Data from different experiments on central nervous system (CNS) oxygen toxicity in humans in the hyperbaric chamber ($n = 661$) were analyzed along with data from actual closed-circuit oxygen diving ($n = 2{,}039$) by using a maximum likelihood method. The parameters of the model were solved for the combined data, yielding the power equation for active diving: $K = t^2 (P_{O_2}/101.3)^{6.8}$, where t is in minutes. It is suggested that the risk of CNS oxygen toxicity in diving can be derived from the calculated parameter of the normal distribution: $Z = [\ln(t) - 9.63 + 3.38 \times \ln(P_{O_2}/101.3)]/2.02$. The recovery time constant for CNS oxygen toxicity was calculated from the value obtained for the rat, taking into account the effect of body mass, and yielded the recovery equation: $K_t = K_e \times e^{-0.079t}$, where K_t and K_e are the values of K at time t of the recovery process and at the end of the hyperbaric oxygen exposure, respectively, and t is in minutes.

hyperbaric oxygen; pulmonary oxygen toxicity; central nervous system oxygen toxicity

HYPERBARIC OXYGEN (HBO) is encountered in clinical treatment in the hyperbaric chamber and in diving. The risk of oxygen toxicity became a prominent issue with the increased use of hyperbaric treatment and the expansion of diving techniques to include oxygen-enriched gas mixtures. However, there is no satisfactory method of calculating the cumulative risk of oxygen toxicity during a HBO exposure. There have been various attempts to quantify the risk of pulmonary oxygen toxicity (9, 15) and central nervous system (CNS) oxygen toxicity. A recent approach of Harabin et al. (18) was to process, in one equation, developing CNS oxygen toxicity, recovery, and the P_{O_2} threshold (with the assumption being that any specified form of oxygen toxicity will not develop below the specified P_{O_2} threshold). However, the toxic process of HBO could differ widely from the recovery process. The toxic process itself, non-steady-state production of reactive oxygen species (ROS) and increased injury, may differ from the steady-state production and removal of ROS, which is the normal state and in which recovery may occur. Therefore, one should not expect that one equation might be applicable to all conditions: developing toxicity, steady state, and recovery. It is not surprising, therefore, that such analyses fail to solve the threshold P_{O_2}, when the parameters of an equation describing both oxygen toxicity and the threshold are solved simultaneously for pulmonary oxygen toxicity (15) and for CNS oxygen toxicity (17). During the past few years, we have developed a quantitative approach to both the toxic process (a power expression) and the exponential recovery (1–3, 6, 7, 22) for the various forms of oxygen toxicity in animals and humans. This approach has been used satisfactorily to interpret various published data and successfully employed to predict the outcome of HBO exposures on CNS oxygen toxicity (6, 7). Because the possibilities of exposing humans to toxic levels of oxygen are limited, our present strategy is to discover the laws of oxygen toxicity in other mammals and to apply them with the appropriate parameters in humans. Some parameters can be derived from human data, and others, by allometric extrapolation, can be derived from other mammals. The main body of data for CNS oxygen toxicity has been derived from the rat, and studying a larger mammal may help refine the parameters selected for humans.

In the present report, we shall introduce the general power equation for any form of oxygen toxicity. We shall continue with a description of its two facets for measurable damage and for all-or-none effects. A description of the exponential recovery will follow. Parameters will be suggested for the reduction in vital capacity (VC), as one example of measurable damage of

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oxygen toxicity. Parameters will also be suggested for CNS oxygen toxicity, as one example of the all-or-none phenomena. To conclude, we shall propose hyperoxic exposure limits for humans.

QUANTITATIVE EXPRESSIONS FOR OXYGEN TOXICITY

Quantification Principles

We assumed that an oxygen-damaged measurable physiological variable (DMG) may have the same relationship with time t and P_{O_2} as the ROS that caused the damage (2). We formulated equations for the kinetics of the main ROS by assuming a non-steady state where the action of scavengers is negligible. On the basis of these equations and the published data on various forms of oxygen toxicity, we propose our two power equations (2, 3).

P_{O_2} Effect

In a previous study (2), we showed that the kinetics of ROS suggest a polynomial relation between ROS production and P_{O_2}. For example, the non-steady-state rate of production of the hydroxyl radical is $d[\cdot OH]/dt = k_2(k_1[X^-][H^+]P_{O_2})^2\ t^3(k_3[Fe^{2+}] + k_4 \times k_1 \times t \times P_{O_2})$, where X^- represents the electron source for oxygen reduction, each k stands for a rate constant, and brackets denote concentration (2). In this example, the highest power of P_{O_2} is 3. The exact form of the equations should be related to the various chemical reactions that produce the specific damage. Because these are not known for each specific form of oxygen toxicity, we chose to use the term with the highest power, assuming it to be the dominant term and, therefore, suggested that $DMG \propto P_{O_2}^c$, where c is the power of the P_{O_2}.

Time Effect

At a constant P_{O_2}, nonlinear regression of the various forms of measurable damage caused by oxygen toxicity, such as reduced VC, blunted hypoxic ventilatory drive, and impaired nerve conduction, showed a preference for a time-squared relation, which agrees with the rate of hydrogen peroxide production in a non-steady state: $d[H_2O_2]/dt = k[X^-]^2\ t^2[H^+]^2\ P_{O_2}^2$ (2). Although H_2O_2 is not the most potent ROS, if its production is the slower process, that will be the rate-limiting factor for other ROS. Therefore, we suggested that $DMG \propto t^2$ (2).

Power Equations

Based on our study of time and P_{O_2} combinations, we suggested a simplified model in which the most effective term is that of the highest power of P_{O_2} (2)

$$DMG = a \times t^2 P_{O_2}^c \quad (1)$$

where a is a constant related to the units of measured damage, and c is for the said damage. The same kinetic principles may be carried over to the all-or-none phenomenon of oxygen toxicity, such as the appearance of substernal pain, convulsions, and death. For these forms of oxygen toxicity, *Eq. 1* was adapted as (3)

$$K = t^2 P_{O_2}^c \quad (2)$$

where K is the cumulative oxygen toxicity index. A symptom may appear when K reaches a threshold value K_c. Each form of all-or-none oxygen toxicity would have a different c and K_c. These power equations agree with various phenomena of oxygen toxicity (2, 3), and it was proven possible to use the algorithm derived (3) to predict CNS oxygen toxicity in the rat as a result of a complex HBO exposure (6, 7).

Complex Exposures

For a complex exposure profile at toxic levels of oxygen, it can be shown (APPENDIX A, *Eqs. A2–A5*) that the cumulative oxygen toxicity indexes, either the parametric DMG or the nonparametric K, follow simple algorithms. In a stepwise exposure [a definite number of intervals (n), each having a selected P_{O_2} ($P_{O_2\,i}$) and exposure duration (t_i)]

$$DMG = a \left\{ \sum_{i=1}^{n} [t_i \times P_{O_{2i}}^{(c/2)}] \right\}^2 \quad (3)$$

$$K = \left\{ \sum_{i=1}^{n} [t_i \times P_{O_{2i}}^{(c/2)}] \right\}^2 \quad (4)$$

For an exposure in which there is a continuous change in P_{O_2} with time, the indexes are solved for their integral forms

$$DMG = a \left[\int_0^{t_{ox}} P_{O_2}^{(c/2)}\, dt \right]^2 \quad (5)$$

$$K = \left[\int_0^{t_{ox}} P_{O_2}^{(c/2)} dt \right]^2 \quad (6)$$

where t_{ox} is the exposure time at a toxic level of oxygen.

Recovery Equations

The power equation, which was developed by using the non-steady-state production of ROS, is valid in this toxic P_{O_2} range. We speculate that, below the toxic level, there could be a neutral level (mostly undefined) at which toxicity ceases to develop any further but at which there is still no recovery either. Below this speculated neutral P_{O_2} range is the range in which recovery from the toxic effect takes place. When the complex exposure also contains a nontoxic P_{O_2}, it is possible to make a recovery calculation.

It has been suggested that recovery from oxygen toxicity in normoxia follows an exponential function for both oxygen toxicity damage and for all-or-none effects (3, 22)

$$DMG_t = DMG_e \times e^{-\tau t} \quad (7)$$

and

$$K_t = K_e \times e^{-\tau t} \quad (8)$$

where DMG_t and K_t are the values of the toxicity indexes at time t of the recovery process, DMG_e and K_e are the values at the end of the hyperoxic exposure, and τ is the recovery time constant. Different manifestations of oxygen toxicity will each have an appropriate time constant. This approach could well describe the recovery of the hypoxic ventilatory drive in rats and the recovery of human VC (22, 13), and, together with the power equation, it has been used successfully to predict recovery from CNS oxygen toxicity in rats when intermittent exposure is used (6).

SELECTING THE PARAMETERS FOR HUMANS

Because the basic processes of toxicity and recovery are common to all mammals, the power equation and the recovery function can be applied to humans with the appropriate parameters, a, c, K_c, and τ, and the variability within each parameter. Two limits of oxygen toxicity are set for human exposure: one related to pulmonary oxygen toxicity and expressed by the reduction in VC, and the other for CNS oxygen toxicity.

Pulmonary Values

There are enough data to derive the parameters for pulmonary oxygen toxicity in the equation $DMG = a \times t^2(P_{O_2}/101.3)^c$. From the data of Clark et al. (11, 12) and Eckenhoff et al. (13), the solved parameters using nonlinear regression are $a = 0.0082$ and $c = 4.57$, where $DMG = \%\Delta VC$ (where ΔVC is the reduction in VC), time t is expressed in hours, and P_{O_2} in kPa. The mean data from those studies, together with the lines solved by the power equation, are shown in Fig. 1. From the data of Eckenhoff et al. (13) and Clark et al. (12), τ was 0.0128, 0.1047, 0.3740, and 0.5437 h^{-1} for P_{O_2} values of 106, 152, 203, and 253 kPa, respectively. Recovery of VC, together with the lines representing the exponential solution, is shown in Fig. 2. When the values obtained for τ were plotted as a function of the P_{O_2} in the preceding hyperoxic exposure, a linear relationship was obtained, such that $\tau = -0.420 + 0.00379\ P_{O_2}$ (Fig. 3). Therefore, the recovery of VC will take the form ΔVC in absolute terms: $\Delta VC_t = \Delta VC_e \times e^{-(-0.42\ +\ 0.00379\ P_{O_2})t}$.

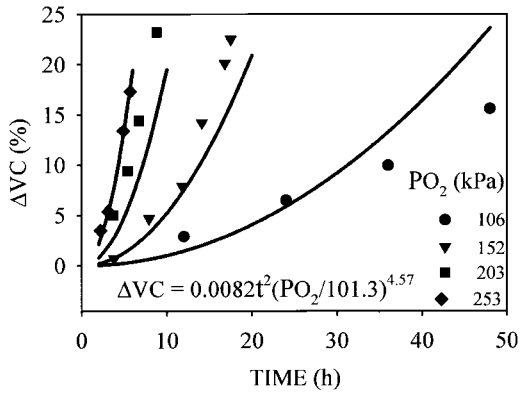

Fig. 1. Reduction of vital capacity (ΔVC) in humans as a function of time (t) and P_{O_2}. Data were taken from Clark et al. (11, 12) and Eckenhoff et al. (13). The lines represent the solution of the power equation.

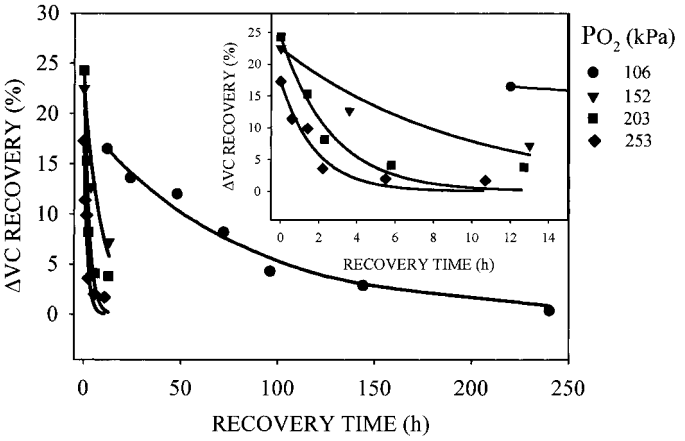

Fig. 2. Recovery of human VC as a function of recovery time and the previous P_{O_2} exposure. Data were taken from Clark et al. (12) and Eckenhoff et al. (13). Recovery took place at a P_{O_2} of 21 kPa, except for the 106-kPa exposure in Eckenhoff et al., when the first 33 h of the recovery process were at 50 kPa. Lines represent the solution of the exponential recovery. *Inset*: recovery after exposure to the three high P_{O_2} values is shown.

As with DMG_e in *Eq. 7*, ΔVC_e is the reduction in VC at the end of the hyperoxic exposure.

In developing our approach to recovery, we assumed that recovery depends on the level of injury, regardless of the time and P_{O_2} that caused this injury. This will be true if identical injury levels have the same rate of recovery, irrespective of how they were produced. It is not surprising, however, that the rate of recovery depends on the P_{O_2} that caused the loss of VC. For the same decrement in VC, other symptoms differed. Severity of pulmonary symptoms (chest pain, cough, chest tightness, and dyspnea) was greater during exposure to 152 and 203 kPa than to 253 and 304 kPa, neutrophil count was greater after 152 kPa than after the 203-kPa exposure, and postexposure arterial P_{O_2} during exercise dropped after exposure to 152 kPa but

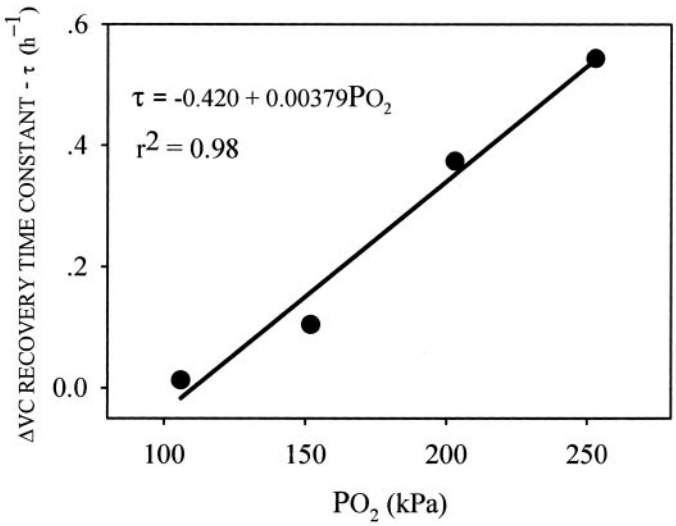

Fig. 3. Time constant (τ) for the recovery of human VC, calculated from the data presented in Fig. 2, as a function of prerecovery P_{O_2} exposure. The line represents the linear regression solution.

not after exposure to 203 or 253 kPa (12). Thus, for the same decrement in VC, the deleterious effects on the lung are related to the pressure at which the insult occurred.

The US Navy recommended oxygen exposure limits that would result in a 2% change in VC and a maximum exposure expected to produce a 10% decrement (20). Thus inserting $\Delta VC = 2\%$ or $\Delta VC = 10\%$ into the power equation will set the P_{O_2} and time limits, and the value of $t^2(P_{O_2}/101.3)^{4.57}$ at a constant pressure or the cumulative value in a complex exposure should not exceed the values 244 and 1,220, respectively.

CNS Oxygen Toxicity Values

Background. POWER EQUATION AND RECOVERY. For CNS oxygen toxicity, the data for convulsions in humans are not sufficient for derivation of the parameters, and the parameters for other models were derived from symptoms other than convulsions (17). We used our data from rats carefully acclimated to the hyperbaric chamber in air, with the maintenance of thermoneutral conditions and a lack of CO_2, to derive the parameters $c = 5.61$ (SE = 0.35) and $K_c = 5.36 \times 10^6$ (SE = 3.18×10^6) ($n = 290$, P_{O_2} range 456–810 kPa, data collected between 1994 and 1999). The mean data and the line representing the prediction of the model are shown in Fig. 4. For the rat, the mean $\tau = 0.31$ min^{-1}, and thus 95% recovery is achieved within 10 min (6).

MODULATORS OF CNS OXYGEN TOXICITY. The two principal modulators affecting CNS oxygen toxicity are metabolic rate and CO_2 load (4, 5). The quantification of these effects was recently studied by us in the rat. We believe that this form of response is common to various mammals with the appropriate parameters. If the power c does not change with alterations in metabolic rate or CO_2, these will be reflected in K_c.

For the metabolic rate effect, CNS oxygen toxicity will develop faster during exercise or when metabolic rate is elevated. This metabolic rate-induced increase in the risk of CNS oxygen toxicity probably involves other known factors, such as cold exposure and high levels of thyroxine (4). We postulated that, at a constant P_{O_2}, the latency to CNS oxygen toxicity decreases linearly as CO_2 production [or oxygen consumption ($\dot{V}_{O_2}$)] increases (4) (Fig. 5, *right*). It is possible to derive K_c at rest (Kc_0) and at an increased metabolic rate (Kc_{ex}). From our experiment, the latency to CNS oxygen toxicity $t = A - B\,\dot{V}_{O_2}$. Inserting this relationship into the power equation yields $(Kc_{ex}) = t^2\,P_{O_2}^c = (A - B\,\dot{V}_{O_2})^2\,P_{O_2}^c$. Therefore the ratio

$$K_{c_{ex}}/K_{c_0} = [(A - B\dot{V}_{O_2\,ex})/(A - B\dot{V}_{O_2\,0})]^2 \qquad (9)$$

where $\dot{V}_{O_2\,ex}$ and $\dot{V}_{O_2\,0}$ are $\dot{V}_{O_2}$ at increased metabolic rate and at rest, respectively. As metabolic rate increases, K_c decreases, which means that the symptoms will appear at a lower combination of time and oxygen pressure. We have shown that both A and B are a function of P_{O_2} (4)

$$A = e^{A_1 - B_1 \times P_{O_2}} \qquad (10)$$

and

$$B = e^{A_2 - B_2 \times P_{O_2}} \qquad (11)$$

Therefore, both parameters A and B decrease with the increase in P_{O_2}.

For the CO_2 effect, an increased level of CO_2 in the inspired gas accelerates the development of CNS oxygen toxicity in humans, as well as in other mammals such as the cat, the rat, and the mouse (5). We have shown in rats that, at a constant toxic P_{O_2}, latency to CNS oxygen toxicity decreases linearly with the increase in inspired P_{CO_2}, down to a latency level from which there is no further reduction in latency with any further increase in P_{CO_2} (5) (Fig. 5, *left*). At a constant toxic P_{O_2} in the P_{CO_2}-dependent range, $t = C - D \times P_{CO_2}$. Replacing t in the power equation will yield $K_{c_{CO_2}} = t^2\,P_{O_2}^c = (C - D \times P_{CO_2})^2\,P_{O_2}^c$, where $K_{c_{CO_2}}$ is K_c at elevated P_{CO_2}. From this expression, the ratio of K_c at elevated P_{CO_2} ($K_{c_{CO_2}}$) to K_c at no CO_2 (K_{c_0}) is as follows

$$K_{c_{CO_2}}/K_{c_0} = [(C - D \times P_{CO_2})/C]^2 \qquad (12)$$

K_c decreases with the increase in inspired CO_2. Both C and D are a function of P_{O_2} (5)

$$c = e^{C_1 - D_1 \times P_{O_2}} \qquad (13)$$

and

$$D = e^{C_2 - D_2 \times P_{O_2}} \qquad (14)$$

Therefore, both parameters C and D decrease with the increase in P_{O_2}. At higher P_{CO_2} values, when latency to CNS oxygen toxicity is reduced but remains constant despite any further increase in P_{CO_2}, it was found in rats that latency to CNS oxygen toxicity $t = e^{C_3} - D_3$ P_{O_2}. The ratio of K_c at the maximal effect of CO_2 ($K_{c_{CO_2\,max}}$) to K_{c_0} is

$$K_{c_{CO_2\,max}}/K_{c_0} = (e^{C_3 - D_3 P_{O_2}}/t)^2 \qquad (15)$$

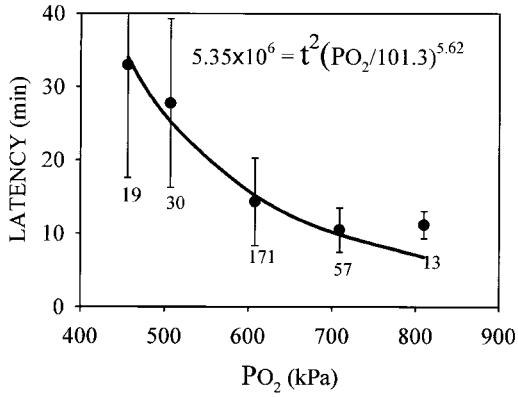

Fig. 4. Latency to central nervous system (CNS) oxygen toxicity in the rat as a function of P_{O_2}. Mean (●) and 2 SD (bars) are shown, together with the no. of measurements. The line represents the power equation.

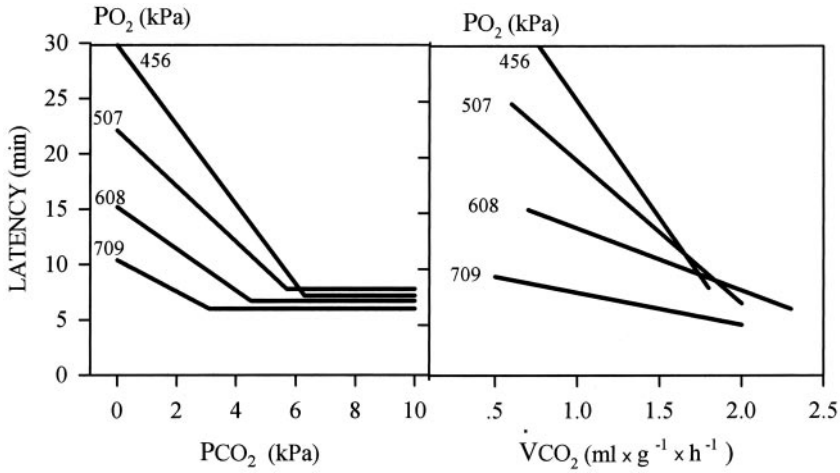

Fig. 5. Latency to CNS oxygen toxicity in the rat as a function of P_{CO_2} and P_{O_2} (*left*) and as a function of CO_2 production ($\dot{V}_{CO_2}$) and P_{O_2} (*right*). The exposure P_{O_2} in kPa is indicated next to the line by which it is represented.

where the term on the *left* is always positive and lower than 1.

VARIABILITY. Our laboratory has shown that there is individual sensitivity to CNS oxygen toxicity in the rat, so that the variability within the rat is much less than the variability between rats (4–7). The prediction of CNS oxygen toxicity based on individual parameters proved superior to employing the group means (7). The issue of individual sensitivity in humans has not been settled yet. Butler and Thalmann (10) suggested that there may be a small number of divers sensitive to CNS oxygen toxicity, although Harabin et al. (16) failed to prove this. However, there are no studies in humans that can be compared with the rat data, which provided clear evidence of individual sensitivity.

RECOVERY TIME CONSTANT IN HUMANS. Because measurements were not made in any other mammals, it would only be reasonable to guess that the use of body mass (BM) might provide us with an approximate solution to the problem. The rate of various physiological processes in mammals (19) is related to BM to the power −0.25. Therefore, the time for 95% recovery in humans should be $10(BM_{rat}/BM_{human})^{-0.25} = 39$ min, and $\tau_{human} = \tau_{rat}\ (BM_{human}/BM_{rat})^{-0.25} = 0.079\ min^{-1}$, where BM_{rat} is rat BM, BM_{human} is human BM, τ_{human} is human τ, and τ_{rat} is rat τ. It is interesting to note that our suggestion agrees with the "rule of thumb" used by Israeli combat divers. Thus, for toxic exposures interspersed with periods of nontoxic P_{O_2}, the reduction in the value of K can be evaluated by using the suggested time constant. Although this time constant was derived from the value measured for the rat, no better approach is available at present.

CNS parameters in humans. The parameters for the power equation can be derived by using the maximum likelihood method for censored observations (APPENDIX B). We extracted those data used by Harabin et al. (17) for exposure to a constant P_{O_2} from all of the data in Harabin's collection (Ref. 14, p. 96–136, compiled from eight different reports, mostly the work of Butler FK and Thalmann ED). The data obtained were from 661 exposures with 3.6% CNS oxygen toxicity symptoms as defined by Harabin et al. (17).

For comparison, we applied the same analysis of CNS oxygen toxicity to our rat data. To the data (n = 290) used for derivation of the power equation parameters for rats, we added exposures to low P_{O_2} when only some rats experienced CNS oxygen toxicity. Thus for a P_{O_2} range of 253–810 kPa, the total data included 395 exposures with 73% CNS oxygen toxicity. The parameters solved for the rat were $c = 6.8$ (SE = 0.2) and $K_c = 6.7 \times 10^7$, $P < 0.0001$ χ^2 for both parameters. The power of P_{O_2} with the data for the 395 exposures, including the low P_{O_2} values, was higher by 1.2 than the value calculated for the data for the 290 exposures for the high P_{O_2} values.

The parameters solved by using the model for human hyperbaric exposures were $c = 15.0$ (SE = 1.8) and $K_c = 5.28 \times 10^9$ ($P < 0.0001$ χ^2 for both parameters and $\sigma = 1.35$). The risk for CNS oxygen toxicity was calculated by using *Eq. B3* in APPENDIX B for the normal distribution

$$Z = [\ln(t) - 11.193 + 7.475 \times \ln(P_{O_2}/101.3)]/1.35 \quad (16)$$

The calculated risk is shown in Fig. 6 as a function of time and P_{O_2} at 1-m depth intervals.

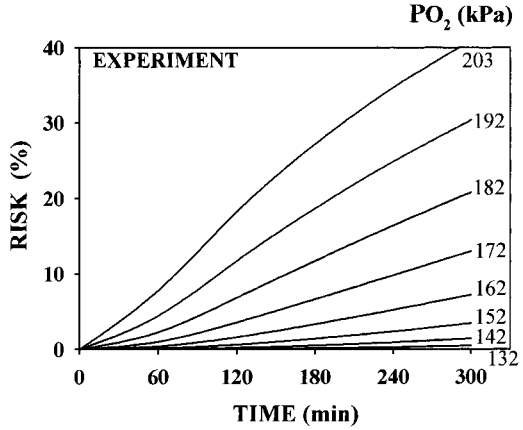

Fig. 6. Percent risk of CNS oxygen toxicity as a function of time and P_{O_2}. The parameters for the calculation were derived from human hyperbaric exposures (14).

We gathered reports of 2,039 closed-circuit oxygen dives from the Israel Navy SEALS. The dives were active training fin dives in the Mediterranean Sea throughout the year at water temperatures ranging from 17 to 28°C. After each dive, the diver completed a form reporting the dive profile and marked a list of symptoms, if any. We measured 98% oxygen concentration in the inspired gas in samples taken during the dives after a few purging procedures and a $\dot{V}O_2$ of 1.4 l/min. Mean depth was 4.2 ± 0.1 (SD) m, and duration was 109 ± 54 (SD) min. Although the percentage of symptoms related to CNS oxygen toxicity in the diving data (3.5%) was similar to that found for the hyperbaric experiments, the maximum likelihood analysis did not yield significant results [χ^2 for a slope of $-c/2$ vs. ln(PO_2) was not significant, $P = 0.93$]. This may be related to the low range of PO_2 (132–162 kPa) for the diving data compared with the hyperbaric experiments (160–250 kPa). We, therefore, took the data from the hyperbaric exposures together with the diving data and applied the maximum likelihood method. The parameters solved using the model for the combined data were $c = 6.8$ (SE = 1.25) and $K_c = 2.31\times10^8$ ($P < 0.0001$ χ^2 for both parameters and $\sigma = 2.02$). The calculation of the normal distribution will now be

$$Z = [\ln(t) - 9.63 + 3.38 \times \ln(PO_2/101.3)]/1.35 \quad (17)$$

It is interesting that the same power c (6.8) was solved for both rats and humans. This may be indicative of a similar process.

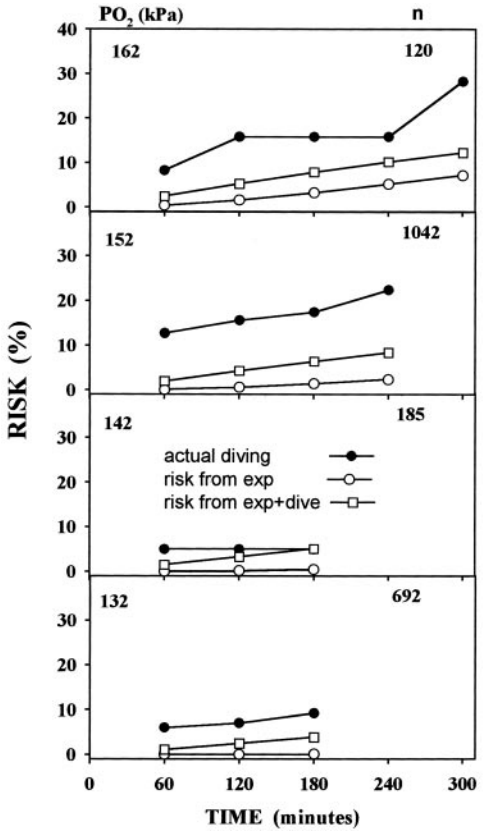

Fig. 7. Percentage of symptoms related to CNS oxygen toxicity (●) in diving as a function of time and PO_2. PO_2 is shown in the *top left* of each panel, and the no. of dives is shown in the *top right*. ○, Risk calculated from the parameters derived from hyperbaric exposures (exp); □, risk calculated from the parameters derived from both hyperbaric exposures and diving.

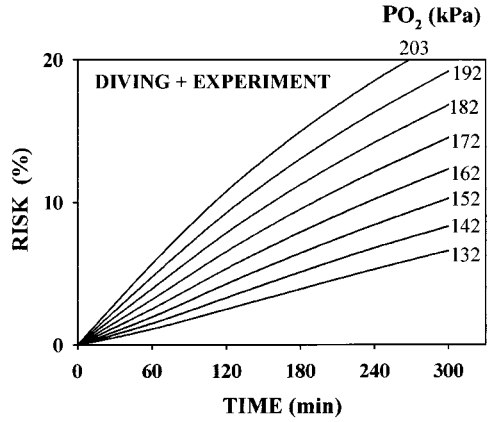

Fig. 8. Percent risk of CNS oxygen toxicity as a function of time and PO_2. The parameters for the calculation were derived from both hyperbaric experiments and diving.

For each diving depth, we calculated the percentage of symptoms at 1-h intervals. The percentage of dives with symptoms during the first hour was added to that for the next hour, and so forth, for calculation of the cumulative risk. This cumulative percentage of CNS oxygen toxicity-related symptoms is shown in Fig. 7, represented by solid circles. We used *Eq. 16* (Fig. 7, open circles) and *Eq. 17* (Fig. 7, open squares) to calculate the risk. The calculated risk using the parameters derived from the hyperbaric experiments is much lower than the actual percentage of symptoms. Underestimation of the calculated risk is also evident in the calculation using parameters from both diving and hyperbaric exposures, but in this case the risk is closer to the actual data.

The dives were active training dives, in which $\dot{V}O_2$ was ~1.4 l/min (8). This $\dot{V}O_2$ is higher than that in the hyperbaric experiments, in which 6 min of exercise (1.3 l O_2/min) were followed by 4 min of rest (17). This protocol would yield a mean $\dot{V}O_2$ of 0.9 l/min. The weighted mean $\dot{V}O_2$ for both diving and experimental data is 1.28 l O_2/min. It is possible that the three lines in each of the panels in Fig. 7 represent the risk at three separate levels of $\dot{V}O_2$.

We used our model with the parameters derived from the hyperbaric experiments and from diving and hyperbaric experiments taken together to calculate the risk within the suggested limits of the United States Navy Single PO_2 Diving Limits (21) (Fig. 8, Table 1). This calculated risk is higher than the calculated risk of Harabin et al. (17), mainly at 25 and 30 ft. When we calculated the time at which 5 or 10% of the divers will experience symptoms related to CNS oxygen toxicity (using both the parameters from the hyperbaric experiments and those

Table 1. *Calculation of the risk of CNS oxygen toxicity within the limits suggested by the US Navy*

Depth, fsw	t, min	Risk Experiments, %	Risk Experiments + Dive, %	Experiments		Experiments + Dive	
				t for 5% risk, min	t for 10% risk, min	t for 5% risk, min	t for 10% risk, min
25	240	13.5	13.4	115	188	82	170
30	80	7.3	6.5	62	101	62	129
35	25	2.9	2.5	35	57	48	99
40	15	3.0	1.8	21	34	38	78
50	10	7.1	1.9	8	13	24	51

Columns 1 and *2,* single P_{O_2} diving limits (21). Parameters used for the model were derived from either hyperbaric experiments (14) or from our diving data and the hyperbaric experiments. The calculated percentage of divers who will experience central nervous system (CNS) oxygen toxicity symptoms is given in *columns 3* and *4.* The time (t) until either 5 or 10% of the divers will experience symptoms is presented in *columns 5–8.* fsw, ft of sea water.

obtained from diving + hyperbaric experiments), the time was less than the suggested limits for 25 and 30 ft.

Two versions of the power equation describing CNS oxygen toxicity in humans were $5.28 \times 10^9 = t^2 (P_{O_2}/101.3)^{15.0}$ for an $\dot{V}_{O_2}$ of 0.9 l/min and $2.31 \times 10^8 = t^2(P_{O_2}/101.3)^{6.8}$ for an $\dot{V}_{O_2}$ of 1.28 l/min. It is too soon to use these two sets of data to derive the complete effect of metabolic rate in humans (*Eqs. 9–11*), and there are no data available that can be used to derive the effect of CO_2 on CNS oxygen toxicity (*Eqs. 12–15*). Further studies using larger mammals may help in the derivation of these expressions using an allometric approach. Calculated limits were determined for the symptoms suggested by Harabin et al. (17): nausea, numbness, dizziness, twitching, hearing and visual disturbances, unconsciousness, and convulsion. However, if some of the milder symptoms, such as dizziness and nausea, are not taken into consideration, the parameters of the power equation will be different. Evidently, the data for humans are far from complete. Some of the reported symptoms may not be related to CNS oxygen toxicity, and the data for real diving were obtained only for the low range of toxic P_{O_2}.

In conclusion, the power equation is a simplified expression derived from the principles of the ROS kinetics. The power equation for cumulative oxygen toxicity and the exponential recovery successfully describe various phenomena of oxygen toxicity. We suggest the use of these expressions to calculate the risk of pulmonary and CNS oxygen toxicity in humans and the rate of recovery.

APPENDIX A

Calculation of Cumulative Oxygen Toxicity When P_{O_2} Is Not Constant

Using *Eq. 1*, let us assume in *step 1* exposure for a time t_1 to a partial pressure of oxygen $P_{O_{2\,1}}$. Then

$$\mathrm{DMG}_1 = a \times t_1^2 P_{O_{2\,1}}^c$$

Let us define t_1' as the time that will produce the same damage as DMG_1 but at a second P_{O_2}, namely $P_{O_{2\,2}}$. Then

$$\mathrm{DMG}_1 = a \times t_1^2 P_{O_{2\,1}}^c = a \times {t_1'}^2 P_{O_{2\,2}}^c$$

from which it follows that

$$t_1' = t_1 (P_{O_{2\,1}}/P_{O_{2\,2}})^{c/2} \qquad (A1)$$

The damage after a second time interval t_2 will be

$$\mathrm{DMG}_2 = a(t_1' + t_2)^2 P_{O_{2\,2}}^c = a[(t_1' + t_2) P_{O_{2\,2}}^{c/2}]^2$$

Replacing t_1' by its value in *Eq. A1*, we obtain

$$\mathrm{DMG}_2 = a\{[t_1(P_{O_{2\,1}}/P_{O_{2\,2}})^{c/2} + t_2] P_{O_{2\,2}}^{c/2}\}^2 = a[t_1 P_{O_{2\,1}}^{c/2} + t_2 P_{O_{2\,2}}^{c/2}]^2$$

The time $t_{2\mathrm{T}}$ at $P_{O_{2\,2}}$ that will yield DMG_2 is

$$t_{2\mathrm{T}} = t_1' + t_2 = t_1(P_{O_{2\,1}}/P_{O_{2\,2}})^{c/2} + t_2$$
$$= t_1(P_{O_{2\,1}}/P_{O_{2\,2}})^{c/2} + t_2(P_{O_{2\,2}}/P_{O_{2\,2}})^{c/2}$$

The expressions

$$\mathrm{DMG}_n = a\left(\sum_{i=1}^{n} t_i P_{O_{2\,i}}^{c/2}\right)^2$$

and

$$t_{n\mathrm{T}} = \sum_{i=1}^{n} t_i (P_{O_{2\,i}}/P_{O_{2\,n}})^{c/2}$$

hold for $n = 2$. Let us assume that this is true for n steps and prove that it is true for $n + 1$.

Let us define t_n' as the time at $P_{O_{2\,n+1}}$ that will produce DMG_n. Then

$$\mathrm{DMG}_n = a t_{n\mathrm{T}}^2 P_{O_{2\,n}}^c = a {t_n'}^2 P_{O_{2\,n+1}}^c$$

from which it follows that

$$t_n' = t_{n\mathrm{T}} (P_{O_{2\,n}}/P_{O_{2\,n+1}})^{c/2}$$

and

$$t_{(n+1)\mathrm{T}} = t_n' + t_{n+1}$$
$$= \left[\sum_{i=1}^{n} t_i (P_{O_{2\,i}}/P_{O_{2\,n}})^{c/2}\right](P_{O_{2\,n}}/P_{O_{2\,n+1}})^{c/2} + t_{n+1}$$
$$= \left[\sum_{i=1}^{n} t_i (P_{O_{2\,i}}/P_{O_{2\,n+1}})^{c/2}\right] + t_{n+1}$$
$$= \sum_{i=1}^{n} t_i (P_{O_{2\,i}}/P_{O_{2\,n+1}})^{c/2} + t_{n+1}(P_{O_{2\,n+1}}/P_{O_{2\,n+1}})^{c/2}$$
$$= \sum_{i=1}^{n+1} t_i (P_{O_{2\,i}}/P_{O_{2\,n+1}})^{c/2}$$

Thus

$$\begin{aligned}\mathrm{DMG}_{n+1} &= a t_{(n+1)\mathrm{T}}^2 \mathrm{Po}_{2\,n+1}^c \\ &= a\left[\sum_{i=1}^{n+1} t_i(\mathrm{Po}_{2\,i}/\mathrm{Po}_{2\,n+1})^{c/2}\right]^2 \mathrm{Po}_{2\,n+1}^c \\ &= a\left\{\left[\sum_{i=1}^{n+1} t_i(\mathrm{Po}_{2\,i}/\mathrm{Po}_{2\,n+1})^{c/2}\right]\mathrm{Po}_{2\,n+1}^{c/2}\right\}^2 \\ &= a\left(\sum_{i=1}^{n+1} t_i \mathrm{Po}_{2\,i}^{c/2}\right)^2 \qquad (A2)\end{aligned}$$

For Po_2 as a continuous function of t, *Eq. A2* yields

$$\mathrm{DMG}_t = a\left(\int_0^{t_{ox}} \mathrm{Po}_2^{c/2}\mathrm{d}t\right)^2 \qquad (A3)$$

For all-or-none effects, DMG should be replaced by K, and the parameter a should be omitted, giving

$$K = \left(\sum_{i=1}^{n+1} t_i \mathrm{Po}_{2\,i}^{c/2}\right)^2 \qquad (A4)$$

or

$$K = \left(\int_0^{t_{ox}} \mathrm{Po}_2^{c/2}\mathrm{d}t\right)^2 \qquad (A5)$$

APPENDIX B

Solution of the Parameters of the Power Equation

The power equation describes the increasing risk of CNS oxygen toxicity as K approaches

$$K_c\colon K = t^2\mathrm{Po}_2^c \qquad (B1)$$

From the available data, in the ith individual exposed to $\mathrm{Po}_{2\,i}$, CNS oxygen toxicity occurs at time t_i. There are individuals in whom toxicity does not occur, so that t_i may be censored. Formally, the observations are given in the following forms

$$(y_i,\ \delta_i,\ \mathrm{Po}_{2i}), \qquad i = 1, \ldots, n, \qquad (B2)$$

where $y_i = \min(t_i, c_i)$, $\delta_i = I_{(t_i \le c_i)}$, and c_i are the censor variables, and δ_i is the indicator showing whether the observation is censored or not. The goal is to fit the censored data (*Eq. B2*) to the model (*Eq. B1*).

Considering t as the response variable, one can write

$$\ln t_i = \tfrac{1}{2}\ln(K_c) + \tfrac{1}{2}c \times \ln(\mathrm{Po}_2)$$

Thus c and K can be estimated by using parametric regression techniques for the survival data. The idea is that

$$Z_i = \frac{\ln(t_i) - (c/2)\ln(\mathrm{Po}_{2i}) - (\tfrac{1}{2})\ln(K_c)}{\sigma}$$

has some distribution f, where $\ln t_i$ can be censored. The likelihood function is written as follows

$$1(c, K_c, \sigma) = \left[\prod_{i:\text{uncensored}} f(Z_i)\right]\left[\prod_{i:\text{censored}} \int_{Z_i}^{\infty} f(x)\mathrm{d}x\right]$$

Then $1(c, K_c, \sigma)$ or $\ln 1(c, K_c, \sigma)$ is minimized over c, K_c, and σ numerically. Distributions for Z_i can be chosen from the following list: *1*) Gausian, $Z_i \sim N(0,1)$; *2*) smallest extreme value, if t has the smallest extreme value distribution, then e^t has a Weibull distribution; and 3) logistic, yields a closed form expression.

In our computations, we used the smallest extreme value distribution. The results obtained are not so sensitive to the choice of f from the above list.

The risk can then be calculated from the normal distribution

$$Z = [\ln(t) - \mu]/\sigma \qquad (B3)$$

$$\mu = \mathrm{E}[\ln(t)] = 0.5\ln(K_c) + (c/2)\ln(\mathrm{Po}_2)$$

where t is in minutes, and Po_2 is in kPa.

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