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ORIGINAL ARTICLE

R. Arieli · A. Gutterman

Recovery time constant in central nervous system O_2 toxicity in the rat

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Abstract The development of oxygen toxicity can be delayed by intermittent periods of normoxia. However, there is no accepted procedure for quantifing the recovery during normoxia. A cumulative oxygen toxicity index - K, when K reaches a critical value (K_c) and the toxic effect is manifested, can be calculated using the equation $K = t_e^2 \times PO_2^c$ where t_e is hyperoxic exposure time and PO_2 is oxygen pressure and c is a power parameter. Recovery during normoxia (reducing K) is calculated by the equation $K_2 = K_1 \times e^{-rt_r}$ where t_r is recovery time, r being the recovery time constant. A combination of accumulation of oxygen toxicity and its recovery can be used to calculate central nervous system oxygen toxicity. In protocol A (n = 25), r was calculated for rats exposed either continuously to 608 kPa oxygen or to PO_2 = 608 kPa followed by a period of normoxia (3.5% O_2), with a subsequent return to PO_2 = 608 kPa until appearance of the first electrical discharge (FED) in the electroencephalogram which precedes clinical convulsions. In protocol B (n = 22), predicted latency to the FED was compared to measured latency for seven different exposures to hyperbaric oxygen (HBO), followed by a period of normoxia and further HBO exposure. Recovery followed an exponential path, with r = 0.31 (SD 0.12) min^{-1}. The predicted latency to FED in protocol B correlated with the measured latencies. Calculation of the recovery of the CNS oxygen toxicity agreed with the previously suggested exponential recovery of the hypoxic ventilatory response and was probably a general recovery process. We concluded that recovery can be applied to the design of various hyperoxic exposures.

Key words High pressure oxygen · Intermittent exposure · Electroencephalogram

Introduction

Prolonged exposure to hyperbaric Oxygen (HBO) is essential in certain situations such as the treatment of diving accidents, as an adjuvant therapy in various clinical conditions, in Nitrox diving and in closed-circuit oxygen diving. Oxygen toxicity [pulmonary as well as central nervous system (CNS) toxicity] is a risk in the continuous use of HBO. It has been reported that the development of oxygen toxicity can be delayed (as a total cumulative oxygen exposure time) by intermittent periods of normoxia (Bleiberg and Kerem 1988; Clark 1993; Harabin et al. 1990). This extension of oxygen tolerance has been found to be related to an increase in the concentration of antioxidants (Clark 1993), however it has been shown that recovery during the normoxic periods may also extend beyond the time at which changes in antioxidant enzymes can be observed (Harabin et al. 1990). This recovery may be related to repairing activity during the normoxic periods. Intermittent air breathing is also employed in hyperbaric oxygen treatment to avoid CNS oxygen toxicity. The choice of the intermittent normoxic intervals has been arbitrary without any clear guiding principle. The ability to quantify recovery could help in constructing an intermittent exposure.

One of the present authors has recently suggested a theoretical approach to the quantification of oxygen toxicity (Arieli 1994a,b). This theoretical approach has been used successfully to calculate cumulative oxygen toxicity and to predict latency to CNS oxygen toxicity in rats (Arieli and Hershko 1994).

We have shown that recovery from oxygen toxicity of the hyperoxic ventilatory drive followed an exponential form (Waisman et al. 1992), as would be expected when the rate of change is related to the magnitude of the change. In the present study, we made use of the pre-

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R. Arieli (✉) · A. Gutterman
Israel Naval Medical Institute, IDF Medical Corps,
POB 8040, Haifa 31080, Israel

viously suggested method for the calculation of cumulative oxygen toxicity and recovery from toxicity (Arieli 1994b; Waisman et al. 1992) to estimate the recovery time constant for convulsions (CNS oxygen toxicity) in the rat. The latter was then used to calculate cumulative oxygen toxicity, and to predict latency to convulsions in exposures composed of two oxygen pressures separated by periods of normoxia.

Successful calculation of cumulative oxygen toxicity and incorporation of recovery periods could yield a method for planning HBO exposures.

Methods

The preparation of the rat and the experimental system have been described in detail (Arieli and Hershko 1994) and only a brief description is outlined here.

Animals

White male Sprague Dawley rats, mean body mass 298 (SD 75) g, had electroencephalograph (EEG) electrodes implanted under pentobarbital anaesthesia (30 $mg \cdot kg^{-1}$, i.p.) 3 days before the experiment. A female miniconnector was soldered to the electrodes. The experimental procedure was approved by the internal Animal care committee and the rats were handled using appropriate international humane standards.

Experimental system and procedure

The miniconnector was mated, and the rat was placed in a thermoregulated Plexiglas cage (3.4 1). The cage was fitted with a thermistor (Yellow Springs Instrument Co., Ohio) for monitoring its ambient temperature. The cage was placed in a 150-1 pressure chamber (Roberto Galeazzi, La Spezia, Italy). The flow of gas through the cage could be checked using a flowmeter installed inside the pressure chamber, and was controlled by a valve outside. When the pressure in the chamber was being raised, the gas flowing through the cage was air. When the desired pressure was reached and the ambient temperature was in the thermoneutral zone of the rat, the air was immediately replaced by pure oxygen. The initial flow of oxygen through the cage was high so that air was replaced by oxygen in 10s. The time at the end of 10-s O_2 flushing was taken as the start of the oxygen exposure. After the oxygen flushing, the flow was reduced to 4 $l \cdot min^{-1}$ (at the actual pressure). Any change in the gas composition of the cage was produced by means of an initially high flow rate (about 20 $l \cdot min^{-1}$) followed by a reduction to 4 $l \cdot min^{-1}$

The rate of compression was 101 $kPa \cdot min^{-1}$. The total time in air from the start of compression until air was replaced by oxygen was 6.7 (SD 2.1) min. The ambient temperature of the cage was 26.7 (SD 1.1)°C. The rat was observed through a window in the pressure chamber for signs of clinical seizure activity. when the first electrical discharge (FED) in EEG, preceding clinical convulsions (Harel et al. 1969), was seen on the recorder (Gould Inc., Cleveland, Ohio), the time was noted and decompression (101 $kPa \cdot min^{-1}$ was commenced. The cage was removed from the pressure chamber and the rat was released.

Protocols

A two-stage protocol was used: protocol A was designed to calculate the recovery time constant, to study its variability, and to validate one aspect of the exponential model by testing its independence of the magnitude of recovery which increases with the duration of the normoxic period. In protocol B, we tested whether the solution could be used to predict latency to FED in an exposure composed of two oxygen pressures with a recovery period between them.

Protocol A

Each rat (n = 25) was exposed sequentially (at least 2 days between exposures) to continuous partial pressure of O_2, (PO_2) = 608 kPa until the appearance of FED at an exposure time defined as t_{FED}, and to a combined exposure with an initial 7 min (defined as t_1) at PO_2 = 608 kPa, a recovery period (defined as t_2) at normoxia (3.5% O_2 balanced by N_2) followed by PO_2 = 608 kPa until the appearance of FED at a time defined as t_3. This procedure is depicted in Fig. 1, where K is the index of cumulative oxygen toxicity, and FED appears when the value K_c is reached. The first normoxic recovery period selected was either 6 or 4 min. The value $(t_1 + t_3 - t_{FED}) / t_1$ may be used as an index for recovery which is independent of the pattern of recovery. This index of recovery ranges from 0 (no recovery) to 1 (complete recovery). When there is no recovery ($t_1 + t_3 = t_{FED}$) the recovery index is 0. As recovery proceeds t_3 increases, with a concomitant increase in the index until eventually, on full recovery ($t_3 = t_{FED}$), the recovery index reaches the value 1. According to the recovery index, other normoxic periods ranging from almost no recovery to full recovery (normoxic periods from 1 to 14 min) were selected for the subsequent exposures. The exposures continued for each rat until detachment of the miniconnector (previous efforts to glue back the miniconnector to the skull failed).

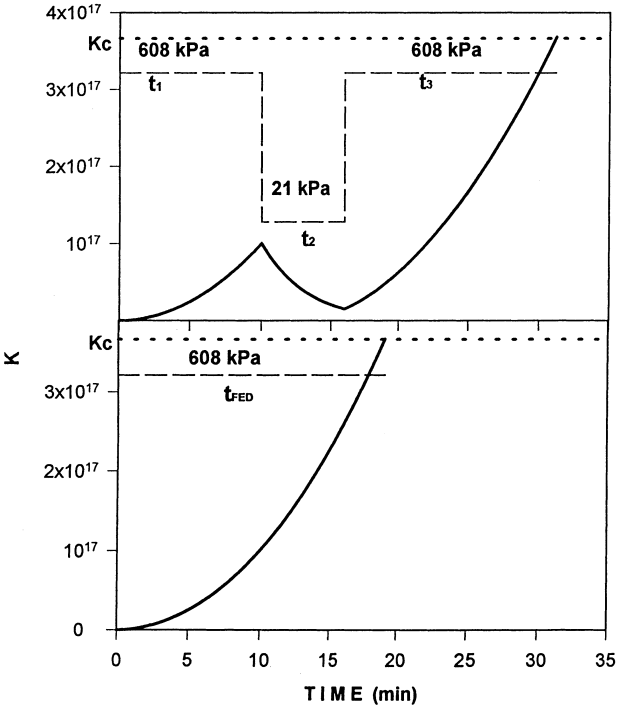

Fig. 1 Protocol for calculation of the recovery time constant. The cumulative oxygen toxicity index K (*heavy line*) is shown as a function of exposure time; K_c (*dotted line*) is the critical value at which convulsions appear. The exposure profile is represented by the *broken line*, with the oxygen pressure indicated *above* and the respective time *below the line*. The *lower panel* represents continuous exposure, and the *upper panel* an exposure with an interim recovery period (t_2), and a second hyperoxic period (t_3) concluded when K intersects with K_c

Protocol B

In protocol B, we exposed each rat (n = 22) to three exposure profiles until the appearance of FED; (1) PO_2 = 709 kPa, (2) PO_2 = 608 kPa, (3) 7 min at PO_2 = 608 kPa, followed by 6-min normoxia and a subsequent return to PO_2 = 608 kPa. These three profiles were used to calculate the power equation parameters (K_c and c in Eq. 1, see calculation in next section) and the recovery time constant (Eq. 2, next section). We then exposed each rat to a series of exposures (until detachment of the miniconnector), each composed of an initial period of high pressure oxygen, a normoxic interval, and a second period at a different high oxygen pressure until the appearance of FED. The pressure change from the first oxygen pressure to the second took place during the intermittent normoxic period. These composite exposures were selected in random order from the seven possible profiles listed in Table 1, and were used to compare predicted latency with the actual results. There were 1.8 (SD 1.4) (range 0–6) composite exposures until detachment of the miniconnector. Data for rats without any composite exposure were used only for calculating the basic parameters.

Calculation of the recovery time constant

In recent reports (Arieli and Hershko 1994; Arieli 1994b) we have suggested that the accumulation of oxygen toxicity that produces at some point all-or-none phenomena obeys the equation:

$$K_e = t_e^2 \times PO_2^c \quad (1)$$

A clinical symptom of oxygen toxicity will appear when K_e reaches a critical value K_c (t_e - exposure time). It has been suggested that recovery from oxygen toxicity (Arieli 1994b) has the form:

$$K_r = K_e \times e^{-rt_r} \quad (2)$$

where r is the recovery time constant per minute, and K_e and K_r are the values of K at the end of hyperoxic exposure and after the recovery period (t_r), respectively. It can be shown (see Appendix) that $r = \{\ln[t_1^2/(t_{FED} - t_3)^2]\}/t_2$

Because t_{FED} was not measured on the same day s t_1 and t_3, we used an average of t_{FED} from the measurements immediately preceding and following those of t_1 and t_3. When there was no measurements of t_{FED} following the composite exposure, only the preceding one was used.

Constraints

The calculation of r for very slight recovery or when recovery was almost completed might have increased the error due to biological variability. Therefore r was not calculated in two conditions:

1. If there was almost no recovery during the normoxic period, the sum $t_1 + t_3$ would equal t_{FED}. When $(t_1 + t_3)/t_{FED}$ was less than 1.10 (less than 10% recovery), the recovery was assumed to be too low to calculate r. However, we did calculate r when $1.05 < (t_1 + t_3)/t_{FED} \leq 1.10$, for the purpose of comparing results from more than 5% recovery to those from more than 10%.
2. If recovery was complete, t_3 would have equalled t_{FED}. As in the previous section, r was calculated when $t_3/t_{FED} < 0.90$ and also when $0.95 > t_3/t_{FED} \geq 0.90$ (either up to 90% recovery or up to 95% recovery).

Table 1 Exposure profiles in series B. Rats were exposed to high oxygen pressure ($PO_{2,\ 1}$) for a determined duration, then to normoxia for a time interval, and thereafter to another high oxygen pressure ($PO_{2,\ 3}$) until the appearance of the first electrical discharge

	$PO_{2,\ 1}$ (kPa)	Time at $PO_{2,\ 1}$ (min)	Time in normoxia (min)	$PO_{2,\ 3}$ (kPa)
1	709	7.0	6.0	507
2	709	7.0	6.0	557
3	608	9.0	10.0	709
4	557	10.0	10.0	659
5	709	7.0	6.0	709
6	709	8.0	3.0	760
7	709	6.0	10.0	507

Calculation of cumulative oxygen toxicity (protocol B)

Because the miniconnector became detached after a certain length of time and after a limited number of exposures, we could not obtain either enough exposures to calculate the parameters of the power equation and recovery (K_c, c and r) for each individual, or a sufficient number of composite exposures to test the predicted latency. Therefore, although using the individually derived parameters for the calculation of latencies to FED in composite exposures should provide better prediction (Arieli and Hershko 1994), for the purpose of comparison we used the mean parameters derived for all the rats in protocol B. We assumed that c = 5.39 (Arieli and Hershko 1994), and calculated K_c from the measured latencies (t_{FED}) to FED in the continuous exposures to 608 kPa and 709 kPa : $K_c = t_{FED}^2 \times PO_2^{5.39}$.

The recovery time constant (r) was calculated as described above. The mean values of K_c and r for all the rats in protocol B were used to calculate the predicted latencies to FED.

In the composite exposures, the expected latency (Δt_3) for the second oxygen pressure was calculated as outlined:
$K_1 = t_1^2 \times PO_{2,\ 1}^{5.39}$, where $PO_{2,\ 1}$ and t_1 are the initial oxygen pressure and the time spent at that pressure.
$K_2 = K_1 \times e^{-rt_2}$, where t_2 is the normoxic time,
$t_3 = (K_c/PO_{2,\ 3}^{5.39})^{0.5} - (K_2/PO_{2,\ 3}^{5.39})^{0.5}$, where $PO_{2,\ 3}$ is the second high oxygen pressure.

Statistics

The Pearson correlation coefficient was used to compare measured and predicted latency. Nonlinear regression was used to fit the exponential function to the recovery index (see text for definition) and ANOVA with repeated measures (SAS institutes, Cary, N.C.) was used to compare r for different normoxic times.

Results

Protocol A

There were 5.7 (SD 2.1) exposures (range 2–12) for each rat until detachment of the miniconnector. As in our previous report (Arieli and Hershko 1994), the preceding exposures had not effect on latency to FED (t_{FED}) in the subsequent continuous exposures, rats gained body mass during the experimental time, and no ill effects were observed. The mean latency (t_{FED}) was 16.4 (SD 8.1) min. Of the total 60 composite exposure (in 25 rats), 25 exposures (in 16 rats) were in the 10%–90% recovery range, while 34 exposures (in 20 rats) were in the range 5%–95%. Thus r was calculated for 20 rats in the 5%–95% recovery range and for 16 rats in the 10%–90% recovery range. The recovery index is shown in Fig. 2 as a function of the time spent in normoxia. In theory, for exponential recovery, the recovery index should be defined by the equation: $(t_1 + t_3 - t_{FED})/t_1 = 1 - e^{-0.5rt_2}$.

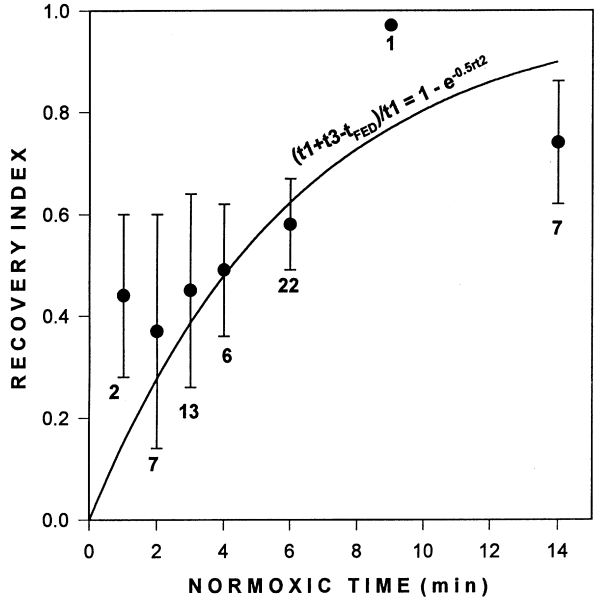

Fig. 2 Recovery index as a function of the normoxic recovery time. Data are shown as mean and SEM with the number of data *indicated below the symbol*. The *line for the exponential increase* in the recovery index as solved for all the data is also given with the equation. For parameters, see Fig. 1

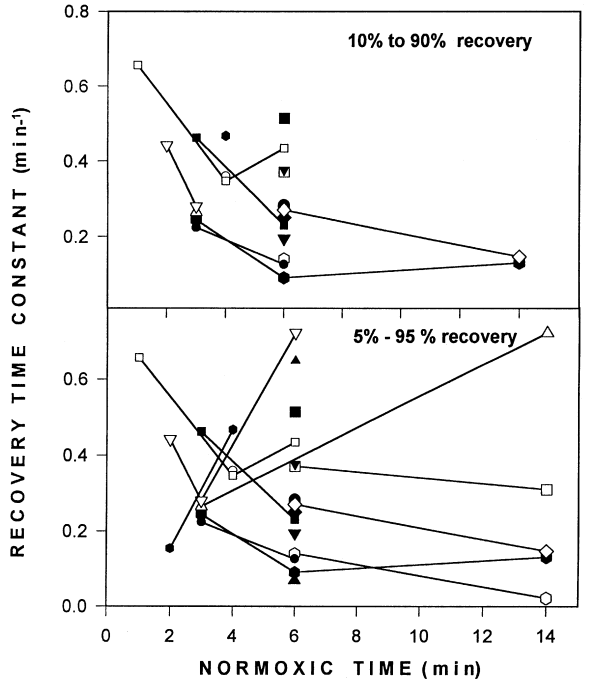

Fig. 3 Recovery time constant plotted against the time in normoxia for either 10%–90% recovery (*upper panel*) or 5%–95% recovery (*lower panel*). Different symbols (*pattern and size*) represent individual rats. Data from the same rat are *connected by a line*

We used a nonlinear regression to fit an exponential recovery index to the individual data, and the line representing the solution is also shown. Because errors may be large at very small recovery or at high recovery, there are some deviations from the calculated function at the extreme ranges (1 and 14 min). The mean recovery index reaches 50% at 5-min normoxia and 90% at 14 min, while the calculated mean recovery time constant is $0.33 \cdot \text{min}^{-1}$ (note that the time constant for index of recovery is half the recovery time constant).

In the exponential recovery process (Arieli 1994b; Waisman et al. 1992) the calculation of the recovery time constant will be independent of the extent of the recovery. However due to intra-animal variability, there may be an error in calculation at either very slight or very great recovery. We give all the recovery time constants for either 10%–90% or 5%–95% recovery as a function of recovery time in Fig. 3. The mean recovery time constant for 16 rats calculated in the 10%–90% recovery range is 0.31 (SD 0.12) min^{-1}. The magnitude of the time constant does not depend on the recovery time either for the whole group or for each individuum (see line connecting symbols). The calculated time constant falls within a higher range for 5%–95% recovery than for 10%–90% recovery due to inevitable error in this range (see constraints).

Because we were able to take three calculations of the time constant from only a few rats, we compared variability in rats having at least two calculated time constant (n = 10). Of the three values obtained for 3 rats, we selected the two which were within 15%–85% recovery. Analysis of variance of r with repeated measures (short and long normoxic interim) revealed no difference between the time constants measured for a short time in normoxia and that measured for a longer normoxic time. No effect was found when time constants were compared in relation to the sequence of the exposures. Individual time constants did not show any trend (increasing or decreasing), even on the 6th–8th exposures. The within-animal variability in r was 46% of the total variability where 54% was due to between animals.

Protocol B

The mean and SEM measured latency to FED for the second high oxygen pressure is plotted against the predicted latency for the seven possible composite exposures, together with the exposure used for the calculation of r, in Fig. 4. The line of regression (dotted line, Fig. 4) calculated for all the data (n = 62, correlation coefficient = 0.39, $P < 0.01$, slope significantly different from 0, $P < 0.005$) did not differ significantly from the line of equality (solid line, Fig. 4).

Discussion

Critique of the method

We have suggested (Arieli 1994b) that there is an exponential recovery from oxygen toxicity in general and

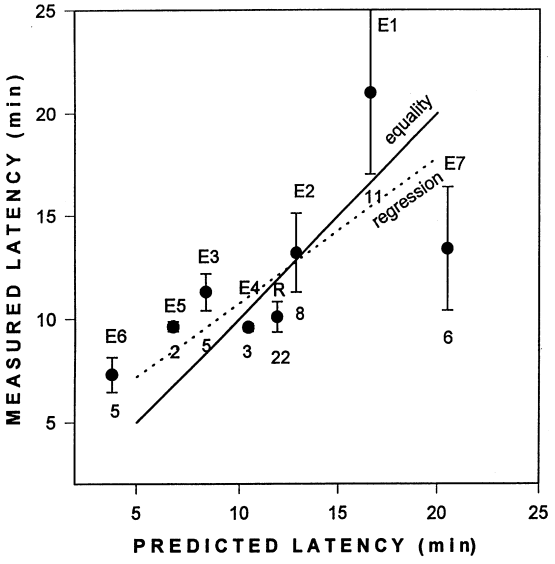

Fig. 4 Measured latency to first electrical discharge (mean and SEM) for the second high oxygen pressure plotted against predicted latency for an exposure consisting of an initial high oxygen pressure followed by a period in normoxia and a second high oxygen pressure. The exposure profile (from Table 1) is indicated by *E* and a number (*R* represents the exposure for calculation of the recovery time constant). The number of data is shown *below the symbol*. The *solid line* is the line of equality and *the dotted line* is the linear regression

have shown experimentally its validity for hypoxic ventilatory drive (Waisman et al. 1992). This is also true in the specific case of recovery from CNS oxygen toxicity. The within-animal variability of the recovery time constant was similar to the between-animal variability (Fig. 3), and was different from the low within-rats variability with regard to the parameters of the power equation (Arieli and Hershko 1994). Using the power equation for the calculation of cumulative oxygen toxicity and the exponential recovery, we successfully calculated latency to FED for an exposure composed of two high oxygen pressures separated by a normoxic period. This was accomplished using the mean parameters for the power equation and the recovery time constant, because due to detachment of the miniconnector, we could not obtain a sufficient number of composite exposures to derive reliable parameters for each animal. Most probably, if we had been able to derive the parameters for each rat, the correlation between predicted and measured latencies would have increased.

Sensitivity

Individual sensitivity to high oxygen pressure will be expressed by the individual latency to FED: short latency implies high sensitivity. Similarly, fast individual recovery is related to a high r value. There was no correlation between individual latency to FED at PO_2 = 709 kPa and the individual recovery time constant for any rat in either protocol, A or B, i.e. there was no relationship between individual sensitivity to oxygen toxicity and the rate of recovery.

Application of the recovery

This tool for the calculation of both cumulative oxygen toxicity and the recovery from oxygen toxicity may be employed in various applications. Harabin et al. (1988), referring to the protection from O_2 toxicity by intermittent normoxic periods, have stated that "little is known about how it works". The rate of recovery may be related to the declining oxygen free radicals, to the building up of the level of inhibitory transmitters like GABA, to the recovery of the control of cerebral blood flow and other suggested pathways in the generation of HBO-induced seizures (Torbati 1995). The above principles may be used to calculate the optimal intervals of hyperoxia and normoxia.

In certain situations where there is a need for prolonged exposure to HBO, it would be of advantage to be able to extend the hyperoxic time while reducing the risk of oxygen toxicity. Previous studies, summarized by Clark (1993) have shown that intermittent alternate exposure to hyperoxia and normoxia will extend the total time in hyperoxia until the appearance of symptoms of oxygen toxicity. No strict guidelines were followed in selecting the combination of hyperoxic and normoxic periods. The parameters used to calculate the development of oxygen toxicity and the recovery time constant may also be used to suggest an intermittent exposure. For example, from the data of Eckenhoff et al. (1987) on the recovery of vital capacity (*VC*) from a PO_2 = 106 kPa exposure, we used nonlinear regression ($\Delta VC_r = \Delta VC_e \times e^{-r \times t_r}$, where t_r = recovery time) to calculated the recovery time constant as 0.13 h^{-1}. Similarly, from the combined data of Lambertsen (1989) for the recovery of VC from hyperoxic exposures to 152, 203 and 253 kPa, we calculated the recovery time constant as 0.11 h^{-1}. Using data calculated earlier for cumulative oxygen toxicity (Arieli 1994a), the equations for cumulative ΔVC and recovery of VC in percentages are: $\Delta VC_e = 0.0064 \times PO_2^{4.94} \times t_e^2$ and $\Delta VC_r = \Delta VC_e \times e^{-0.12 \times tr}$, where subscripts *e*, and r stand for the hyperoxic exposure and recovery, respectively (PO_2 in ATA). One may use these equations to construct an intermittent exposure to delay the decrease in human VC.

There are possible long-term effects of exposure to oxygen, which appear after the time required for almost complete recovery. In 14 min of normoxia, there was almost complete recovery for CNS oxygen toxicity in the rat (Fig. 2). With a 1-day interval between exposures, however, latency to FED increased between the fourth and the sixth exposures (Lavy et al. 1973), though a 2-day interval between exposures had no effect on latency (Arieli and Hershko 1994). Repeated exposure to PO_2 = 405 kPa in sequence over a period of 3 days has been shown to sensitize rats to CNS oxygen toxicity (Fenton and Robinson 1993). Therefore, although re-

covery from the acute symptoms of toxicity can continue up to 20 min, another effect may last for a day and disappear after 2 days.

Closed or semi-closed circuit oxygen diving is usually limited by depth and time. Short deep excursions have to be compensated for by returning to a shallow depth to reduce the risk of CNS oxygen toxicity. The length of time required for this is not based on any clearly defined principle. The principles for calculating cumulative oxygen toxicity and recovery can also be used for oxygen diving. The parameters for the power equation can be derived from a compilation of the exposures to HBO in which subjects have experienced some form of CNS oxygen toxicity. The recovery time constant in humans is not yet known.

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Appendix

Calculation of recovery time constant
From Eq. 1, the latency to FED is:

$$t_{\mathrm{FED}}^2 = K_c / PO_2^c = A_c \quad (3)$$

Because we used a single high PO_2, we can define a parameter A for the division of the cumulative oxygen toxicity index by oxygen pressure to the power c. The composite exposure consisted of an initial exposure of t_1 to PO_2 = 608 kPa, followed by a normoxic period of t_2, and a second exposure to PO_2 = 608 kPa lasting t_3 until appearance of FED.

From Eq. 1 , at the end of the first hyperoxic exposure the value of K is:

$$K_1 = t_1^2 \times PO_2^c \text{ and}$$

$$t_1^2 = K_1 / PO_2^c = A_1 \quad (4)$$

After the recovery period, K decreases according to Eq. 2:

$K_2 = K_1 \times e^{-rt_2}$, and when both sides of the equation are divided by PO_2^c we obtain:

$$A_2 = A_1 \times e^{-rt_2} \quad (5)$$

In the second hyperoxic exposure, the appropriate time $t_{0,3}$ at which K_2 would be reached on continuous exposure (Arieli 1994b) is:

$$t_{0,3} = (K_2 / PO_2^c)^{0.5} = A_2^{0.5} \quad (6)$$

At the end of the second exposure, on appearance of FED the value K_c is obtained:

$$K_c = (t_{0,3} + t_3)^2 \times PO_2^c \quad (7)$$

Rearranging Eq. 7 and using Eq. 3 yields:

$$(t_{0,3} + t_3)^2 = K_c / PO_2^c = A_c \quad (8)$$

From Eqs. 6 and 8:

$$t_{0,3} = A_c^{0.5} - t_3 = A_2^{0.5}$$

and $A_2 = (A_c^{0.5} - t_3)^2$. Substituting A_c from Eq. 3 gives:

$$A_2 = (t_{\mathrm{FED}} - t_3)^2 \quad (9)$$

By substituting the values for A_1 from Eq. 4 and for A_2 from Eq. 9 into Eq. 5, one obtains:

$$(t_{\mathrm{FED}} - t_3)^2 / t_1^2 = e^{-rt_2}$$

and the value of r can be derived as:

$$r = \{ln[t_1^2 / (t_{\mathrm{FED}} - t_3)^2]\} / t_2$$

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