Original articles

Calculated risk of pulmonary and central nervous system oxygen toxicity: a toxicity index derived from the power equation

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Abstract
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Background: The risk of oxygen toxicity has become a prominent issue due to the increasingly widespread administration of hyperbaric oxygen (HBO) therapy, as well as the expansion of diving techniques to include oxygen-enriched gas mixtures and technical diving. However, current methods used to calculate the cumulative risk of oxygen toxicity during an HBO exposure i.e., the unit pulmonary toxic dose concept, and the safe boundaries for central nervous system oxygen toxicity (CNS-OT), are based on a simple linear relationship with an inspired partial pressure of oxygen (PO_2) and are not supported by recent data.
Methods: The power equation: Toxicity Index = $t^2 \times PO_2^c$, where t represents time and ^{c} represents the power term, was derived from the chemical reactions producing reactive oxygen species or reactive nitrogen species.
Results: The toxicity index was shown to have a good predictive capability using PO_2 with a power ^{c} of 6.8 for CNS-OT and 4.57 for pulmonary oxygen toxicity. The pulmonary oxygen toxicity index (PO_2 in atmospheres absolute, time in h) should not exceed 250. The CNS-OT index (PO_2 in atmospheres absolute, time in min) should not exceed 26,108 for a 1% risk.
Conclusion: The limited use of this toxicity index in the diving community, after more than a decade since its publication in the literature, establishes the need for a handy, user-friendly implementation of the power equation.

Introduction

Hyperbaric oxygen (HBO) is encountered during clinical treatment in the hyperbaric chamber and in diving. The risk of oxygen toxicity has become a prominent issue due to the increasingly widespread administration of HBO therapy, as well as the expansion of diving techniques to include oxygen-enriched gas mixtures and technical diving. But there is still no satisfactory method of calculating the cumulative risk of oxygen toxicity during an HBO exposure. The concept of the unit pulmonary toxic dose (UPTD), which is based on a modification of the rectangular hyperbola, was proposed in response to a request for oxygen exposure limits based on a very small amount of research data: a point at four atmospheres absolute (atm abs) (405.2 kPa) and the absence of known injury at an inspired partial pressure of oxygen PO_2 of 0.5 atm abs (50.6 kPa). It was merely descriptive, without any basis in physico-chemical or physiological mechanisms (Lambertsen 1990, personal communication).

In light of all this, it was clear that a different model was required to fit outcome data. The power law approach was adopted for this study. The power equation derived from the chemical reactions related to PO_2 which produce reactive oxygen species (ROS) and reactive nitrogen species (RNS) was shown to have good predictive capability.[1,2] The main difference between the power equation and the rectangular hyperbola is the high power of PO_2 in the former: 6.8 for central nervous system oxygen toxicity (CNS-OT); and 4.57 for pulmonary oxygen toxicity (P-OT). At a high PO_2, the rectangular hyperbola will lose its predictive power. Many researchers and physicians continue to use the UPTD model,[3,4] even where it can be shown not to match reality. The recommended boundaries for avoiding CNS-OT vary between different agencies and lack validation. The present report proposes a handy, user-friendly implementation of the power equation, provides corroboration for other measures of P-OT, and suggests preliminary CNS-OT limits at rest to complement those for conditions in which there is physical exertion.

THE POWER EQUATION AND OXYGEN TOXICITY

The power equation takes the form:

$$Toxicity\ Index = K = t^2 \times PO_2^c \quad (1)$$

where t represents time in hours or minutes, PO_2 is expressed in atm abs, and ^{c} represents the power term (specified above).

Data from 2,700 individual reports (2,039 closed-circuit oxygen active training dives at 1.2–1.6 atm abs (121.6–162.0 kPa) with a water temperature of 17–28°C, and 661 immersed hyperbaric exposures at 1.6–2.5 atm abs (162.0–253.2 kPa) with subjects exercising) were used to derive the power expression for CNS-OT, thus facilitating a maximum likelihood analysis.[1] The power expression for POT was derived from the reported means in resting dry hyperbaric exposures,[5–7] and therefore, as in the UPTD concept, the threshold for severity of the exposure is presented regardless of variability.

Rate of recovery was assumed to be in proportion to the severity of injury, which leads to the exponential equation (common in recovery from many injuries):

$$\text{Toxicity Index}_{tr} = \text{Toxicity Index}_{e} \times e^{-\tau \times tr} \quad (2)$$

where the subscript e represents the end of the hyperoxic exposure, tr is the recovery period, and τ is the time constant.

In principle, no threshold was incorporated in the power expression, which operates when ROS and RNS production overpowers antioxidant activity.[1] In a dry chamber saturation dive at 450 metres' sea water (msw) for 210 h, followed by 51 h at 360 msw, and with an inspired PO_2 of 0.5–0.6 atm abs (50.6–60.8 kPa),[8] part of the deterioration in lung function could be ascribed to P-OT. The calculated P-OT index was 4,433, which is very high. It is suggested that, in prolonged exposures with a relatively low PO_2, a recovery process may accompany the development of P-OT to attenuate but not entirely eliminate the toxic outcome. In CNS-OT, the threshold between the development of toxicity and recovery is between an inspired PO_2 of 1.2 and 1.3 atm abs (121.6–131.7 kPa).

PULMONARY OXYGEN TOXICITY

The derived power equation for the loss of vital capacity (VC) in our previous work was:[1]

$$\Delta VC\% = 0.0082 \times t^2 \times (PO_2)^{4.57} \quad (3)$$

where t is the time in hours and inspired PO_2 is expressed in atm abs.

Exponential recovery of pulmonary oxygen toxicity took the form:

$$\Delta VCtr\% = \Delta VCe\% \times e^{-[-0.42 + 0.384 \times (PO_2)_{ex}] \times tr} \quad (4)$$

where tr is the recovery time in hours, ΔVCtr is the value after the recovery time, ΔVCe is the value following the previous hyperbaric oxygen exposure, and $(PO_2)_{ex}$ is the previous inspired PO_2 exposure in atm abs. The rate of recovery depends on the PO_2 which caused the insult and is effective from exposure to a PO_2 > 1.1 atm abs (111.4 kPa). The value of the time constant at 1.1 atm abs may be used for PO_2 < 1.1 atm abs.

For a square exposure (at a constant inspired PO_2), to determine the expected decrement in VC, Eq. 3 applies. For a complex exposure, during which PO_2 varies and recovery periods at oxygen pressures below 0.50 atm abs, a complex calculation is required. For a number of periods (*n*) of continuous hyperoxic exposure, each for a different length of time and at a different PO_2, the calculation should take the form:

$$\Delta VC\% = 0.0082 \times [\sum_{i=1}^{n} ti \times (PO_2 i)^{2.28}]^2 \quad (5)$$

When the PO_2 changes continuously with time, Eq. 6 should be used:

$$\Delta VC\% = 0.0082 \times [\int_0^{tox} (PO_2 i)^{2.28} dt]^2 \quad (6)$$

where *tox* is the total time in hyperoxia.

When there is a recovery period in between the hyperoxic exposures, ΔVC% at the end of recovery should be calculated from Eq. 4. The time required to obtain the same ΔVC% for the next PO_2 (PO_2nx) in the hyperoxic exposure will then be derived by rearranging Eq. 3 thus:

$$t^* = [\%\Delta VC / (0.0082 \times (PO_2 nx)^{4.57})]^{0.5} \quad (7)$$

This calculated time t* should be added to the time of the coming hyperoxic period, as if the whole exposure started from this PO_2.

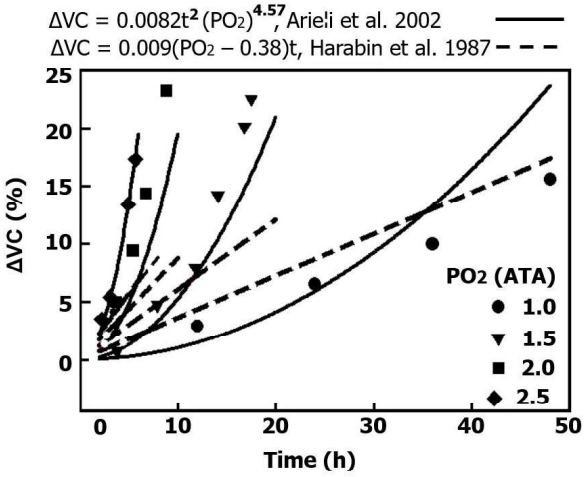
A comparison of the prediction provided by the power equation (present study) and the UPTD approach is shown in Figure 1. The adjusted reduction in VC predicted by UPTD[4] fails to follow the the measured data.[5–7]

The US Navy recommended oxygen exposure limits that will result in a 2% change in VC, maximum exposure being expected to produce a 10% decrement.[3] Thus, inserting ΔVC = 2% or ΔVC = 10% into the power equation will set the PO_2 and time limits. For these two values of ΔVC, the pulmonary oxygen toxicity index $t^2 \times (PO_2)^{4.57}$ should not exceed 244 and 1,220, respectively, both at a constant pressure and for a complex exposure. This index is proposed as a replacement for the UPTD concept. With regard to the UPTD concept, a study which conducted a thorough examination of the various models concluded that "*the UPTD model should not be used except for steady exposures to* PO_2 *of approximately 1 ATA and for times up to 1000 min*".[9]

A recently published study[10] suggested other measures (incidence of symptoms, incidence of changes in forced vital capacity (FVC), forced expiratory volume25-75 (FEV_{25-75}), forced expiratory volume in one second (FEV_1), or diffusing

Figure 1

Prediction by two models of the reduction in pulmonary vital capacity at four oxygen pressures as a function of time: the Naval Medical Research Institute modified pulmonary toxicity dose (broken lines), and the P-OT index (solid lines). ATA = atmospheres absolute pressure. Reproduced (with modifications) with permission from reference 1



capacity for carbon monoxide (DLCO) to replace changes in VC in the evaluation of P-OT. Because the units of the P-OT index are squared for time and the powered PO_2, this index can also accommodate other estimates. A comparison of the two methods is provided in Figure 2.

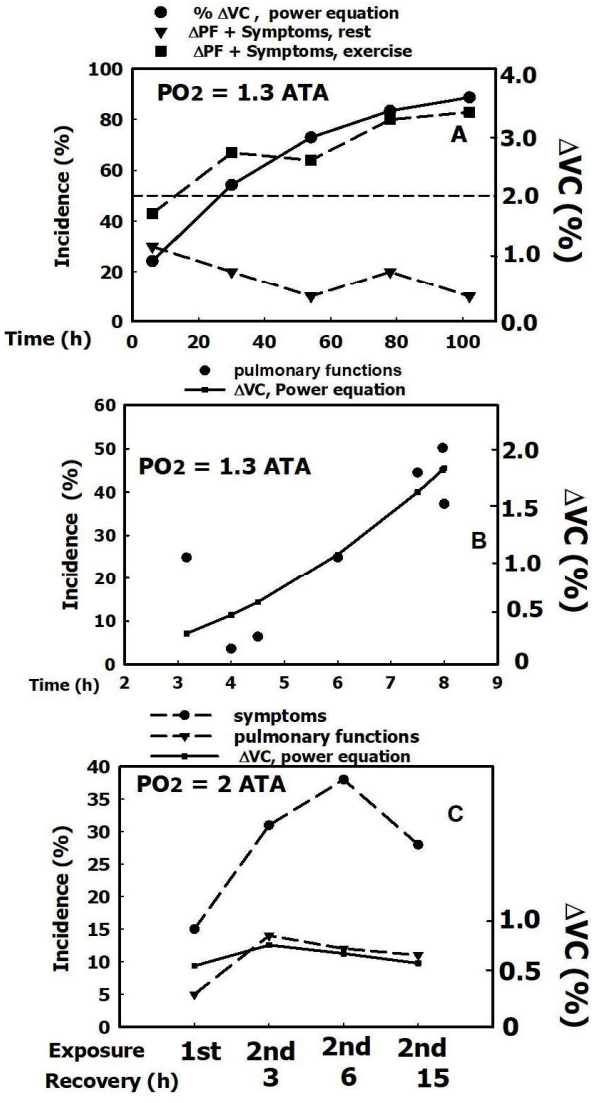
Divers made five consecutive daily dives for six hours breathing either oxygen at 1.3 atm abs or air.[11] The present author subtracted the percentage of divers who had either pulmonary symptoms or reduced volume flow after the air dives from the percentage of divers suffering from symptoms or reduced flow after the oxygen dives, taking this difference as the percentage of divers with pulmonary oxygen toxicity. The percentage of divers with P-OT after remaining at rest or performing moderate exercise during the dive is plotted against time in Figure 2A. The reduction in VC as calculated using the oxygen toxicity index, which takes into account accumulation and recovery at the end of each O_2 exposure, is also shown. It can be seen that the ΔVC calculated using the toxicity index correlates with the number of divers with P-OT during exercise; a condition in which toxicity is more prevalent. This also reinforces our approach to recovery.

In another study,[12] groups of exercising divers were exposed to 1.3–1.4 atm abs (131.7–141.8 kPa) inspired PO_2 for variable times; the incidence of P-OT is plotted in Figure 2B together with the calculated ΔVC. Agreement can be seen between the incidence of P-OT and the ΔVC calculated from the toxicity index.

In the previously mentioned study,10 subjects were exposed to 2 atm abs (202.6 kPa) O_2 in a dry chamber for 3 h, and again to the same protocol after recovery periods of either

Figure 2

Percentage of divers with P-OT symptoms (inspiratory burning, cough, chest tightness and dyspnoea), pulmonary function (PF) parameters (FVC, FEV_{25-75}, FEV_1) or their combination (symbols and dashed lines), and the calculated reduction in VC obtained using the P-OT index (solid lines). Evaluation conducted after: A) Five consecutive daily dives at rest or exercising for 6 h (PO_2 = 1.3 atm abs).[10] B) Single dives (exercise, 1.3 atm abs O_2) for different lengths of time;[11] C) A single dive (3 h, 2 atm abs O_2), and a second dive under the same conditions after a recovery period of 3, 6 or 15 h;[12] Five consecutive daily dives at rest or exercising for 6 h (PO_2 = 1.3 atm abs).[10] Note the agreement between the incidence of P-OT and the ΔVC calculated using the P-OT index. ATA = atmospheres absolute pressure



3, 6 or 15 h. The incidence of P-OT is shown together with the calculated ΔVC in Figure 2C. A good correlation is seen between the incidence of P-OT and the calculated ΔVC. The P-OT index can thus predict both ΔVC and the incidence of P-OT, which strengthens the argument for its use in determining exposure limits.

Table 1
P-OT index (K) calculated for exposures to 2 atm abs oxygen until termination due to the severity of pulmonary symptoms. Data from Widell et al[13]

Exposure	O_2 time (h)	Total time (h)	K
Continuous	5.8	6	799
25 min O_2, 5 min air breaks	8.2	9.8	1,154
20 min O_2, 20 min air breaks	6.9	13.8	412
10 min O_2, 20 min air breaks	5.1	15.4	145

In another investigation,[13] subjects were exposed to 2 atm abs oxygen either continuously or with intermittent air breathing until termination due to severe P-OT (Table 1). The P-OT index was calculated for these exposures. For continuous exposure, 25 min O_2 breathing periods with 5 min air breaks, and 20 min O_2 breathing periods with 20 min air breaks, the toxicity index was between 412 and 1,154, which is within the suggested range of 244–1,220 for a 2% and 10% ΔVC. Only for a fourth condition (10 min periods of O_2 breathing with 20 min air breaks) was a low toxicity index (145) noted. This could be related to the fact that the last protocol had the longest total exposure time of 15.4 h. It may be that mild symptoms of P-OT cannot be tolerated over such a long time.

Therefore, it is proposed that ΔVC be replaced by the P-OT index for the measurement of P-OT. Thus, to calculate the P-OT index (K), the multiplication by 0.0082 may be omitted from Eq. 3, 5 and 6, ΔVC will be replaced by K in Eq. 3, 4, 5 and 6, and Eq. 7 will be replaced by $t^* = [K/(PO_2nx)^{4.57})]^{0.5}$. In summary, it is suggested that for the most common exposures the P-OT index limit be set at 250.

CENTRAL NERVOUS SYSTEM OXYGEN TOXICITY (CNS-OT)

It is clear that in diving the risk of CNS-OT must also be taken into consideration. The various symptoms related to CNS-OT (nausea, numbness, dizziness, twitching, hearing and visual disturbances and convulsions)[1,14] were used for the calculations. These symptoms were shown to precede loss of consciousness underwater during exposure to a PO_2 of 1.5 to 1.6 atm abs (152.0–162.0 kPa).[15]

The power equation for CNS-OT was similar in form to that derived for P-OT:

$$K = t^2 \times (PO_2)^{6.8} \quad (8)$$

where K is the *CNS-OT index*, t is the duration of the hyperoxic exposure in minutes, and PO_2 is expressed in atm abs. Risk is related to the magnitude of K.

Recovery of CNS-OT risk will occur when the diver is exposed to a PO_2 below 1.3 atm abs. The exponential recovery expression is:

$$Ktr = K_e \times e^{-0.079 \times tr} \quad (9)$$

where the subscript e represents the end of the hyperoxic exposure and tr is the recovery period in min.

In a complex hyperbaric exposure comprising a number of periods of hyperoxia (in excess of 1.3 atm abs), the following two expressions (similar to those derived for P-OT) may be used for a sequence of distinct pressures and for a continuous function of PO_2 with time, respectively:

$$K = \cdot[\sum_{i=1}^{n} ti \text{ x } (PO_2i)^{3.4}]^2 \quad (10)$$

$$K = \cdot[\int_0^{tox} (PO_2i)^{3.4}dt]^2 \quad (11)$$

When there is a recovery period in-between the hyperoxic exposures, K should be calculated from Eq. 9. The time required to obtain the same K for the next PO_2 (PO_2nx) in the hyperoxic exposure will then be derived by rearranging Eq. 8 thus:

$$t^* = [K / (PO_2nx)^{6.8}]^{0.5} \quad (12)$$

This calculated time t* should be added to the time of the coming hyperoxic period, as if the whole exposure started from this PO_2.

Risk calculation

Risk calculation may be derived from the standard normal probability using the *CNS-OT index,* which is the value K derived for a specific dive profile:

$$Z = [\ln(K^{0.5}) - 9.63] / 2.02 \quad (13)$$

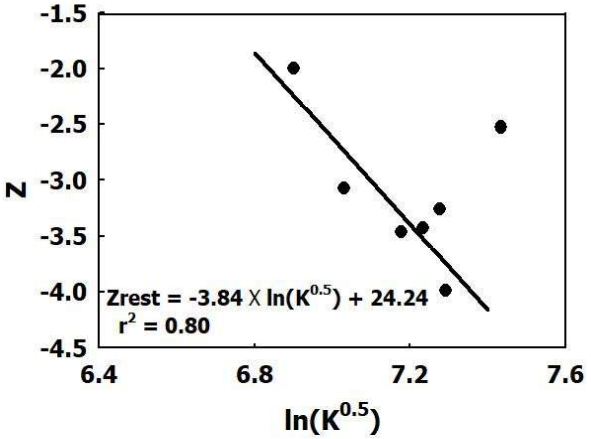
The desired risk limit may be determined by rearranging Eq. 13 thus:

$$K = [e^{2.02 \times Z + 9.63}]^2 \quad (14)$$

This enables one to find the *CNS-OT index* for the selected risk. For example, the *CNS-OT index* should not exceed 58,571 for a 2% risk, 196,811 for a 4% risk, and 432,700 for

Figure 3

The corresponding risk value Z in resting conditions, plotted as a function of the logarithm of the square root of the *CNS-OT index* (calculated using the exercise parameters); data taken from different sources (references in the text). Results of the linear regression are also shown



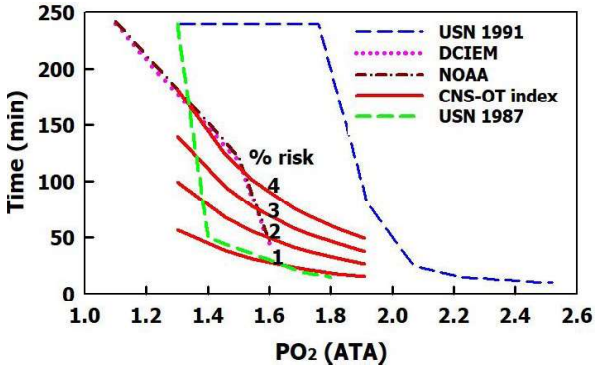
a 6% risk. The data used for the power equation were from divers exercising with an O_2 consumption of approximately 1.3 L·min^{-1}.[1,2] One must, therefore, expect a greater or lesser risk than that selected due to any alteration in metabolic rate above or below 1.3 L·min^{-1} and hypercapnia.[1] For deep diving, a low risk should be adopted.

The parameters derived for exercise were used to examine resting conditions. In US Navy Treatment Table 6 (USN TT6), calculating the toxicity index for the first three 20-min oxygen breathing periods and the two intervening 5-min recovery periods breathing air gave the values at the end of each stated period (× 10^5): 4.6 (first oxygen breathing period), 3.1 (first air break), 15.2 (second oxygen breathing period), 10.3 (second air break), and 28.7 (third oxygen breathing period). The maximum level after the third oxygen breathing period at 2.83 atm abs (286.7 kPa) corresponds to that stage in the treatment at which most of the convulsions were reported.[16] However, the *CNS-OT index* calculated for the reported incidence of 0.56% from one hyperbaric treatment facility was 7.6 times that for a calculated risk of 0.56% with exercise at 1.3 L·min^{-1}. In a similar vein, the German Navy reported a 3% incidence of CNS oxygen toxicity in their oxygen tolerance tests,[17] but the calculated *CNS-OT index* was 28 times the value for exercise with the same 3% risk. It would appear that a higher *CNS-OT index* may be tolerated in resting conditions.

For an estimation of the *CNS-OT index* at rest, data were collected from reported HBO exposures in resting conditions.[16–20] K was calculated from the exposure profiles, and based on our finding of a linear relationship between Z and ln($K^{0.5}$),[1,2] Z for the appropriate incidence is plotted against ln($K^{0.5}$) in Figure 3. Most of these data refer to seizures rather than the preceding symptoms. The equation thus derived for the value of Z (excluding one extreme point,

Figure 4

Permissible exposure to hyperoxia (PO_2/time) to avoid CNS oxygen toxicity in diving; data from different institutes. Both 1987 and 1991 US Navy recommendations are shown. The calculated percentage risk using the *CNS-OT index* is also shown



calculated for USN TT6)[16] is:

$$Zrest = -3.84 \times \ln(K^{0.5}) + 24.24 \quad (15)$$

Caution will be required when using this equation, because the parameters of the power equation were derived for exercise. Therefore, this equation can be used only as a preliminary approximation. Evidently, increased risk should be related to an increase in the index of toxicity. It now remains to solve the power equation for hyperoxic exposure at rest in the same way we did,[1] using the vast amount of individual data that has been amassed. When that is completed, we will be able to exclude from HBOT patients having a clinical condition that sensitizes them to CNS-OT, or desensitize them perhaps by means of a ketogenic diet. With the newly derived power, we should see the slope in Figure 3 change sign. The present analysis supports the general applicability of the power equation and the *CNS-OT index*.

Discussion

The PO_2/time limits calculated using the *CNS-OT index* for active diving are compared with other commonly employed limits in Figure 4. There is a vast difference between the US Navy limits in 1991[21] and those promulgated in 1987, and those of the National Oceanographic and Atmospheric Administration (NOAA) and the Defense and Civil Institute of Environmental Medicine (DCIEM),[22] with the Israeli Navy limits positioned somewhere in between those of the NOAA and the US Navy in 1991. The assumption of a linear relationship with PO_2 for the purpose of establishing the NOAA boundaries[22] evoked the comment: "*These limits were based on best judgment from extensive experience, not on the statistical analysis of quantitative data*."[23] In a summary of the Duke University and US Navy models, the same authors concluded: "*Thus, while oxygen toxicity models are useful for illustrating principles, predictions for partial pressures of 1.6 atm or less are unreliable at best*."[23] The

limits calculated using the *CNS-OT index* for a 1% risk are close to the US Navy's 1987 limits (Figure 4). Therefore, it is suggested that the *CNS-OT index* should not exceed 26,108.

The predictive power of the *CNS-OT index* was proved in complex exposures which had not been included in the calibration procedure.[2] It has been used for planning excursion dives in the Israeli Navy, and has been proposed for use in the Royal Netherlands Navy.[24] It has also been used in the calculation of safe submarine escape procedures in both humans and goats,[25,26] and was successfully employed in the prediction of convulsions in the resting rat.[27,28] Acclimation to hyperoxia is a factor which also requires to be taken into consideration, as shown in dives using closed-circuit oxygen apparatus.[14] Thus, experienced oxygen divers may safely adopt a higher *CNS-OT index* compared with the unacclimated diver. The proposed boundaries for any chosen percentage risk are for any symptom of CNS-OT, and it should be borne in mind that convulsions and loss of consciousness in Israeli Navy divers (3–6 msw), generally follow the appearance of several milder symptoms.[15]

Conclusions

The oxygen toxicity index is based on the suggested chemical reactions which produce ROS and RNS, and its correlation with the insult of oxygen toxicity should allow a reasonable level of predictive validity. It is proposed as a superior alternative to existing methods of calculating the safe PO_2/time boundaries for oxygen toxicity.

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