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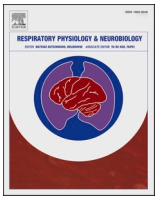

The pulmonary oxygen toxicity index

R. Arieli [a,b,*]

[a] Israel Naval Medical Institute, Haifa, Israel
[b] Eliachar Research Laboratory, Western Galilee Medical Center, Nahariya, Israel

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ABSTRACT

Pulmonary oxygen toxicity (POT) is a major risk in diving while breathing hyperoxic gas and is also considered in clinical hyperbaric oxygen treatment. The POTindex calculated by the power equation $K = t^2 \times PO_2^{4.57}$ with the recovery form $Ktr = Ke \times e^{\frac{1}{2x}}$ [illegible] $0.42 + 0.384 \times (PO$ which are based on chemical and physiological principles, have a better prediction power than other suggested approaches. Reduction of vital capacity as well as incidence of POT are well predicted by the POTindex. Both the cumulative pulmonary toxic effect and concomitant recovery were suggested to operate at the lower toxic range of PO_2 used in saturation diving $K = t^2 \times PO_2^{4.57} \times e^{-0.0135 \times t}$, and further experimental support is supplied. The recovery time constant for the full range of PO_2 is presented. POTindex is suggested to replace the old method of UPTD for safe diving. Many diving clubs and diving institutes already adopted the POTindex.

1. Introduction

Exposure to high partial pressure of oxygen (hyperoxia) is common in diving and clinical hyperbaric treatments. One risk in hyperoxic exposure is pulmonary oxygen toxicity (POT). Half a century ago, Bardin and Lambertsen (1970) suggested the UPTD concept, which was derived from the rectangular hyperbola as a measure for risk of pulmonary oxygen toxicity. The rectangular hyperbola was not derived from physiological principles but from limited data – a point at PO_2 of 4.5 bar and extended tolerance to 0.5 bar oxygen (Lambertsen personal communication). Over the years few modifications were made including raising the time to a power of 1.2 (Wright, 1972). The UPTD concept transforms the effects of oxygen at 1 bar to higher PO_2 in a single unit of 1 bar.

$$UPDT = t \times [(PO_2 - 0.5) / 0{\cdot}5]^{1/1{\cdot}2}$$

This measure had been accepted in the US Navy (U.S. Department of the Navy, 2018). Longstanding efforts of research to quantify POT have been conducted ever since, resulting in different approaches to quantify POT (Hills, 1976, 1977; Harabin et al., 1987; Shykoff, 2007, 2015). However, UPTD prevailed until recently, despite its questionable efficiency, and calls to terminate the use of this method of calculation (Shykoff, 2017). 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 atmosphere absolute (ATA) and for times up to 1000 min" (Shykoff, 2007). A recent publication which thoroughly examined all other models suggested a "Farewell to UPTD" and recommended the use of the POTndex (Risberg and van Ooij, 2022). Later on, they suggested for practical approach to use equivalent surface oxygen toxicity (ESOT) as the square root of POTindex (Risberg et al., 2023). Recent publications presented agreement of the findings on pulmonary oxygen toxicity with the POTindex but not with the UPTD predictions (Brenna et al., 2023; Hadanny et al., 2019; Lian et al., 2022). The Diving Medical Advisory Committee has recently suggested the use of POTindex in its square root expression -ESOT (Diving Medical Advisory Committee, 2023).

2. Power equation, exponential recovery and oxygen toxicity index

Consideration of the kinetics of chemical reactions producing reactive oxygen species (ROS) and reactive nitrogen species (NOS) yielded the understanding that the reaction can be expressed in polynomial expression of the partial pressure of oxygen (PO_2). Because we do not know the full exact reactions, we assumed that the reaction is related to the highest power of PO_2 as a first approximation. It was also found that a measurable injury due to oxygen toxicity is related to a square time. The time relationship of one of the initially produced ROS - H_2O_2, is also correlated with the squared time (Arieli, 1994, 2019a, 2019b; Arieli et al., 2002). Thus, the index of oxygen toxicity (K) was determined by

* Correspondence to:12 Klil-Hakhoresh, Rakefet, D.N. Misgav, 2017500, Israel.
E-mail address: arieli1940@gmail.com.

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the power equation $K = t^2 \times PO_2^c$ (1).

t = time, c= specific power for a specific injury. It was assumed (like other recoveries from injury) that the rate of recovery at non-hyperoxic PO_2 is related to the level of the injury. This led to an accepted form of exponential recovery:

$$Ktr = Ke \times e^{-\tau \times tr} \quad (2)$$

tr =recovery time, Ktr = POTindex after recovery, Ke = POTindex before recovery, τ = recovery time constant h^{-1}.

When there are few sections of hyperoxic PO_2, the index of oxygen toxicity can be calculated with the following equation:

$$K = [\sum_{i=1}^{n} ti \times (PO2i)^{c/2}]^2 \quad (3)$$

For a continuous change in PO_2 with time, the index of oxygen toxicity can be derived with the integral form:

$$K = [\int_0^{tox} (PO2)^{c/2} dt]^2 \quad (4)$$

When there is a recovery period between separate hyperoxic exposures, Ktr should be calculated from Eq.2. The time required to obtain the same Ktr for the next PO_2 (PO_2nx) in the hyperoxic exposure will then be derived by rearranging Eq. 2 thus:

$$t^* = [Ktr / (PO_2nx)^c]^{0.5} \quad (5)$$

For the calculation of K after the exposure to PO_2nx, t * should be added to the time in the next hyperoxic PO_2, as if the whole exposure initiated at PO_2nx.

This approach enables the calculation of K for any complex hyperoxic exposure including recovery periods. The descriptive and predictive capacity of the index of oxygen toxicity has proven valuable in central nervous system oxygen toxicity and POT in both animals and humans (Arieli, 1994b, 1994a, 2003, 2019a, 2019b; Arieli and Gutterman, 1997; Arieli and Hershko, 1994; Arieli et al., 2002).

3. Pulmonary oxygen toxicity index – POTindex

For the calculation of the magnitude of units in any specific injury an adjusting constant – "a" should be added to the power equation:

$$a \times K = a \times t^2 \times PO_2^c \quad (6)$$

The reduction in vital capacity (ΔVC) was chosen by Bardin and Lambertsen (1970) to quantify injury in POT. Using the data from the reported studies (Clark et al., 1991, 1999; Eckenhoff et al., 1987) we solved the parameters of Eq. 6 (Arieli et al., 2002).

$$\Delta VC = 0{\cdot}0082 \times t^2 \times PO_2^{4.57} \quad (7)$$

Where, ΔVC is the absolute change in % of vital capacity, t is the time in h, and PO_2 is the partial pressure of oxygen in bar. Harabin et al. (1987) tested the various modification of the rectangular hyperbola including powered time to solve the best formula predicting reduction in vital capacity. Her best solution was a rectangular hyperbola where the threshold was 0.38 but not 0.5 bar. A comparison of the best fit for the rectangular hyperbola (Harabin et al., 1987) to the power equation (Arieli et al., 2002) is shown in Fig. 1. Lines calculated with the power equation (red) are closer to the measured data as compared to the rectangular hyperbola calculations (blue). Superiority of the power equation on the rectangular hyperbola is clearly seen. Recovery of ΔVC at non-hyperoxic PO_2 was taken from Eckenhoff and Clark studies (Clark et al., 1991, 1999; Eckenhoff et al., 1987) and is shown in Fig. 2, including the lines represent the solved exponential recoveries. Recovery took place at a PO_2 of 0.21 bar O_2, except for the 1.1 bar exposure when the first 33 h of the recovery process were at 0.5 bar O_2. The time constant τ (h^{-1}) was linearly related to the level of the exposed PO_2 before the recovery (Arieli et al., 2002) as is shown in Fig. 3.

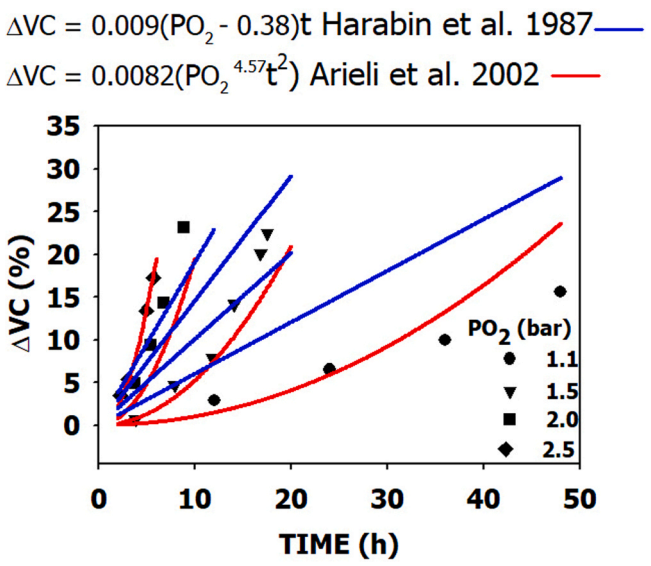

Fig. 1. Reduction of vital capacity (ΔVC) in humans (adapted and corrected from ref. 12) as a function of time (t) and PO_2. Data were taken from Clark et al., (1991, 1999) and Eckenhoff et al. (1987). The red lines represent the solution of the power equation and blue line represent the UPTD concept (Harabin et al., 1987).

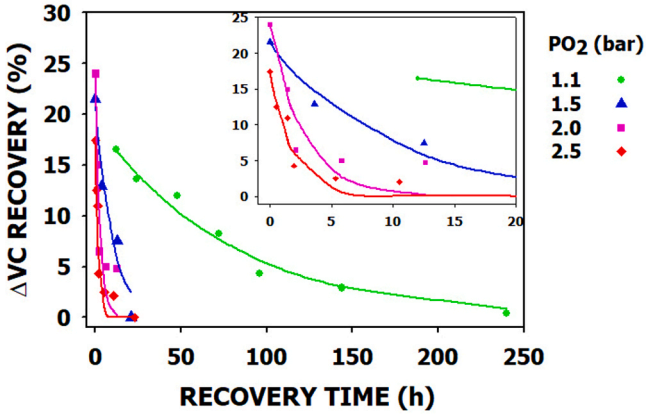

Fig. 2. Lines represent the solutions of the exponential recovery. Inset-expansion of the three high PO_2 from the main figure.
Recovery of human VC as a function of recovery time and the previous PO_2 exposure (adapted from Arieli et al., 2002).

$$\tau = -0{\cdot}42 + 0{\cdot}384 \times PO_2 ex \quad (8)$$

The change in recovery time constant for different exposed PO_2 can be explained by the nature of pulmonary injury. It was shown in rats that increasing PO_2, resulted in a higher involvement of the central nervous system to POT (Demchenko et al., 2007, 2011). Thus, exponential recovery of VC takes the form:

$$\Delta VCtr\% = \Delta VCe\% \times e^{\frac{1}{2ex} \times -0{\cdot}42 + 0{\cdot}384 \times (PO} \quad (9)$$

ΔVCe and ΔVCtr = difference of VC before and after recovery, tr= recovery time, $PO_2ex = PO_2$ at exposure before recovery. Eqs. 8 and 9 should not be used for PO_2 below 1.1 bar.

More recently, symptoms (inspiratory burning, cough, chest tightness, dyspnea), reduced volume flows (FEV_1, FEV_{25-75}, FVC) and DLCO were suggested as more sensitive measures of POT (Shykoff, 2002, 2014, 2015; Shykoff and Florian, 2018; van Ooij et al., 2011). Because the units of the POTindex are squared for time and the powered PO_2, this

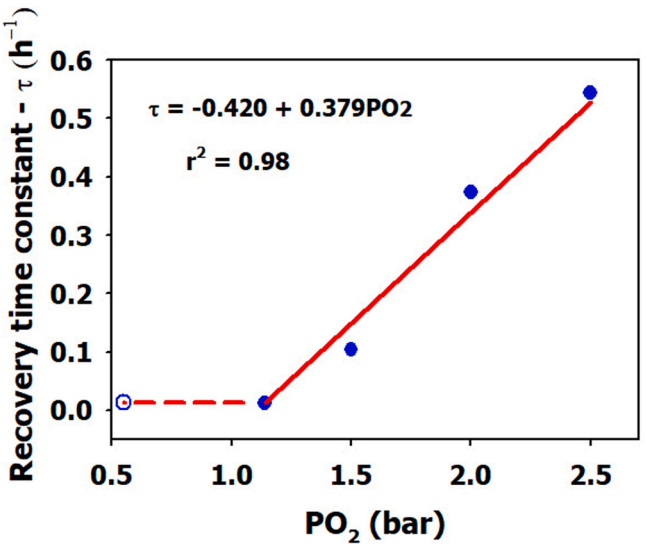

Fig. 3. Time constant (τ) for the recovery of human VC (filled blue circles) calculated from the data presented in Fig. 2, as a function of pre-recovery PO_2 exposure. The line represents the linear regression solution (Arieli et al., 2002). Empty blue circle represents the time constant calculated for saturation dive and the dashed line stands for the suggested leveling off τ at low PO_2s (see Section 6).

index can also accommodate other estimates. Incidence of POT in few experiments are plotted as a function of time or sequence together with calculated change in VC using the power equation in Fig. 4. The calculated values of ΔVC (red lines and symbols) follow the measured incidence of other pulmonary toxic parameters (blue lines and symbols), which support the generality of the POTindex. The percentage incidence of POT in three reported studies (16 different exposures) at a PO_2 of 1.3 or 2 bar, with or without periods of recovery, at either exercise or resting conditions (Shykoff, 2014, 2015; Shykoff and Florian, 2018), is plotted in Fig. 5 as a function of our calculated POT index. A linear relationship may be seen between incidence of POT and the POTindex according to the equation:

$$\text{POT incidence } \% = 1{\cdot}85 + 0{\cdot}171 \times \text{K}\cdot \quad (10)$$

$r^2 = 0.88$.

Regardless of the PO_2 during exposure and the recovery periods, the POTindex will determine the incidence of POT. Compared to the significant difference in the effect of exposure time /PO_2 on central nervous system oxygen toxicity between dry and immersed conditions (Aviner et al., 2020), no effect of dry and wet exposures was found in POT incidence (Shykoff, 2005). CNS oxygen toxicity is also affected by the metabolic rate (Arieli, 1998) but POT is not. This reinforces the generality of expression 10 (rest-exercise; wet-dry).

4. Establishing the limits of POTindex

According to the calculations based on Eq. 10, the incidence of POT in 10 % of the divers will occur when K = 48 and in 20 % of the divers when K = 106. Alteration of diffusion capacity was observed in oxygen breathing for 3 h, at 5 m depth with PO_2 of 1.5 bar, K = 57 (van Ooij et al., 2011). However, these insults were mild and could be detected only by thorough physiological testing. They are not alarming symptoms and it is unlikely that they should pose a threat to the diver. The U.S. Navy recommended oxygen exposure limits that will result in a 2 % change in VC, maximum exposure being expected to produce a 10 % decrement (Wright, 1972). 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 POTindex $t^2 \times (PO_2)^{4.57}$ should not exceed 244 and

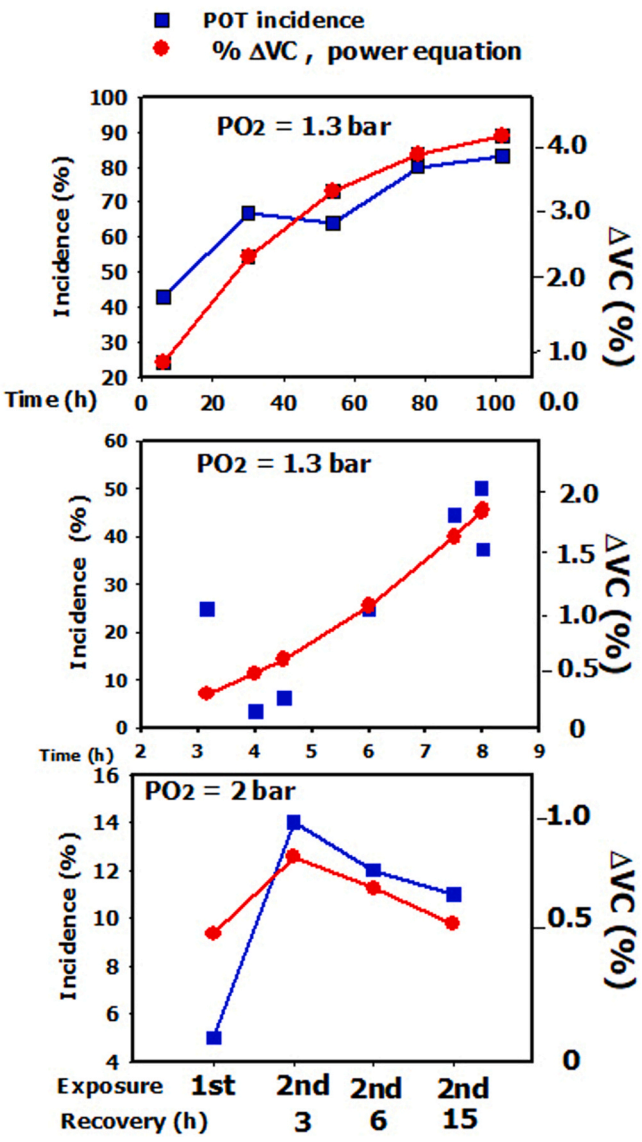

Fig. 4. Percentage of divers with pulmonary oxygen toxicity (POT). Symptoms (inspiratory burning, cough, chest tightness and dyspnea), pulmonary function (PF) parameters (FVC, FEV25–75, FEV1) or their combination (blue symbols and lines), and the calculated reduction in VC (red symbols and lines) obtained using the POT index. Evaluation conducted after: Five consecutive daily dives at rest or exercising for 6 h (PO_2 = 1.3 bar) (upper panel, Shykoff and Florian, 2018). Single dives (exercise, 1.3 bar O_2) for different lengths of time (middle panel, Shykoff, 2015). A single dive (3 h, 2 bar O_2), and a second dive under the same conditions after a recovery period of 3, 6 or 15 h (lower panel, Shykoff, 2014). Note the agreement between the incidence of POT and the ΔVC calculated using the POTindex.

1220, respectively, both at a constant pressure and for a complex exposure. Widell et al. (1974) exposed subjects to 2 bar oxygen either continuously or with intermittent air breathing until termination due to severe POT feeling (Table 1). The POT index was calculated for following exposures: continuous, alternating 25 min O_2 - 5 min air and 20 min O_2 - 20 min air, in which the toxicity index was 412–1154 which is within the suggested range 244 – 1220 for 2% and 10% ΔVC. In the fourth type of exposure monitored in this study, of 10 min O2 – 20 min air K was 145. This could be related to the longest total exposure time of 15.4 h. It is possible that mild symptoms of POT cannot be tolerated in the long run. In a summary, I suggested (Arieli, 2019a) for the most common exposures to set the POT index limit at 250.

In their recent paper, Risberg and van Ooij (2022) suggested lower

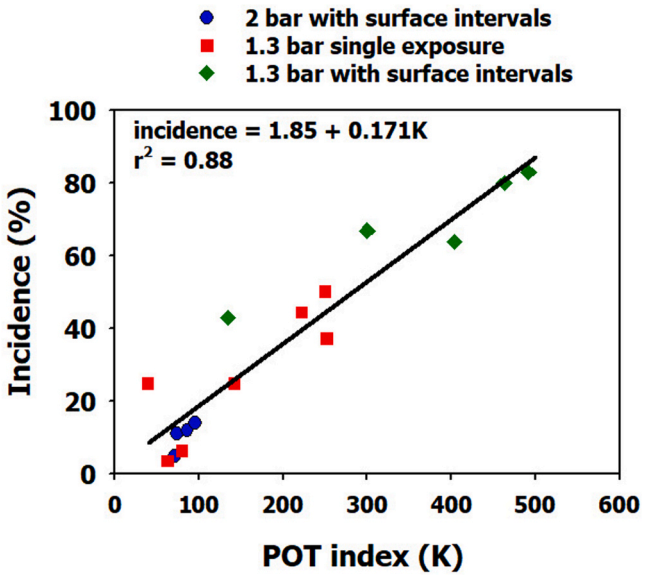

Fig. 5. Incidence of POT (adapted from Arieli, 2019) plotted as a function of the POTindex calculated for each of the 16 different exposures. Regression line is also shown.

Table 1
POTindex – K is calculated for exposures to 2 ATA oxygen until termination when pulmonary symptoms became too severe. Data from Widell et al. (1974).

K	O_2 time, h	Total time, h	exposure
799	5.8	6	Continuous
1154	8.2	9.8	25 min O_2 - 5 min air
412	6.9	13.8	20 min O_2 - 20 min air
145	5.1	15.4	10 min O_2 - 20 min air

limits for K: when diving for up to 2 days, a daily K = 120 followed by two days of recovery. When diving for up to 5 days, K = 70 followed by two days of recovery. For multiday diving without days of recovery, the daily exposure should probably be limited to K = 40–50.

5. POT index in saturation diving (lower range of toxic PO_2)

There is ample information on POT at PO_2 equal or greater than 1 bar, but much less so at lower PO_2. Low PO_2 but still above 0.21 bar is used in saturation diving. An exposure of many days to 0.4 bar O_2 is considered harmless. In saturation diving, divers live in a habitat pressurized to working depth, remaining there for up to several weeks until they are decompressed to surface pressure after completing the work at hand. This method limits the number of decompressions and total time spent decompressing per mission and minimizes the overall risk for decompression sickness.

Saturation diving is usually carried out using heliox breathing mixtures in which the partial pressure of oxygen is maintained at approximately 0.40–0.48 bar, close to the upper limit for long-term exposure (U.S. Department of the Navy, 2018) Although diving bell and lockout operations may also be conducted with a PO_2 of between 0.4 and 0.6 bar, in practice these often employ a PO_2 between 0.6 and 0.9 bar. This serves to attenuate the effect of pressure variations due to excursions away from the holding pressure, thereby reducing the probability and amount of bubble formation which may ensue (Staff Saturation Diving Manual, 2011). Recently received information (Personal communications, Jean Pierre Imbert, Divetech, France and Lyubisa Matity, Hyperbaric Unit, Mater Dei Hospital, Malta.) has attested to saturation holding set typically at a PO_2 of 0.4 bar, and a PO_2 usually somewhere between 0.6 and 0.8 bar during diving and 0.4–0.5 bar in the bell, although some companies do permit 0.9 bar as an upper limit. Decompression is generally carried out at a PO_2 of 0.5 bar.

In 8 different saturation dives made to depths of between 300 and 450 m sea water (msw) for 14–30 days, with a PO_2 of between 0.4 and 0.6 bar (n = 46), chest symptoms and reduced diffusion capacity were ascribed to POT (Thorsen et al., 1994). This change in lung function was attributed to POT because no reduction in lung function was observed with intermittent reduction of the PO_2 during decompression (alternating between 0.5 and 0.3 bar (Thorsen et al., 1990).

For the evaluation of POTindex, from all the reported studies on saturation diving, only one report was found, describing an experimental chamber saturation dive at 450 msw for 210 h, followed by 51 h at 360 msw (a total of 261 h), and with a PO_2 of 0.5–0.6 bar. This report described a deterioration of lung function which was ascribed to POT by Lehnigk et al. (1997). In 2 of the 8 subjects (25%), there was a substantial decrease in pulmonary diffusion capacity. Our calculated POTindex $= t^2 \times (PO_2)^{4.57}$ for 261 h at 0.55 bar O_2, amounts to 4433, which is indicative grave POT, much above the real data. Inserting incidence of 25 % into Eq. 10 yields K = 136. This facilitating search for an expression for POTindex that would yield 136 at 561 h and PO_2 0.55 bar.

We have suggested that recovery may take place simultaneously with prolonged exposure to a low PO_2 (Arieli, 2019b). In comparison with short hyperoxic exposures, the prolonged hyperoxic exposure at low PO_2 dives induce acclimatization to hyperoxia, with considerable changes in gene expression (Kiboub et al., 2018). Four divers were compressed to 45 m for 16 days and further compressed to 70 m for 8 days (Mrakic-Sposta et al., 2020). PO_2 was kept at 0.42 bar and increased to 0.5 at the end of decompression. While working at depth PO_2 was 0.6 – 0.9 Bar. Both total ROS production and antioxidant capacity increased. These two studies support the suggestion that prolonged exposure to low PO_2 affects both the production of ROS and activation of the defense system (recovery).

To adjust these two opposing effects of cumulative toxicity and the recovery process, we assumed that the defense system starts to operate at the beginning of the exposure. The recovery process might in fact be initiated somewhat later in the exposure, but we selected the beginning as first approximation. When more experimental data are available, the equation can be refined accordingly. The following equation may be used:

$$K = t^2 \times PO_2^{4.57} \times e^{-\tau \times t} \quad (11)$$

where t = toxic hyperoxic time in h (with a $PO_2 > 0.48$ bar, (U.S. Department of the Navy, 2018) *PO_2 is in bar, and τ = time constant in h^{-1}.* An even lower hyperoxic limit is possible, because a reduction in pulmonary diffusion capacity was demonstrated with a PO_2 of 0.42 bar in an exposure which lasted 15 days (Suzuki et al., 1991). Using the data from Lehnigk et al. (1997) we solved Eq. 11 for the time constant -, and came up with K = 136 (25% incidence) at the end of the exposure (261 h). The following equation describes the value of K along the exposure:

$$K = t^2 \times PO_2^{4.57} \times e^{-0.0135 \times t} \quad (12)$$

POTindex for the data from Lehnigk et al. (1997) is presented in Fig. 6. The green line represents the compensated (accumulation and recovery) appropriate equation. Evidently, using 8 data points is not enough for an appropriate statistical analysis. However, following the publication of this study (Arieli, 2019b) with the courtesy of Jean Pierre Imbert, he supplied the author with the Lemaire 1975 report. This report describes a 4-day saturation dive, where at 0.6 oxygen, 4 out of 8 subjects (50 %) suffered reduced VC. Using the Eqs. 12 and 10:

$$K = 96^2 \times 0.6^{4.57} \times e^{-0.0135 \times 96} = 244$$

Percentage of pulmonary oxygen toxicity:

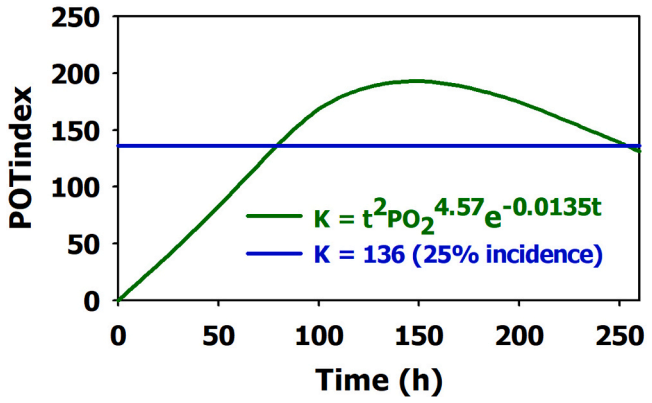

Fig. 6. POTindex (adapted from ref. 33) calculated for the 261 h exposure to a PO_2 of 0.55 bar, for both cumulative toxicity and recovery which take place throughout the exposure (Eq. 12). The recovery time constant is the value which yields K = 136 at the end of exposure, namely 0.0135 h^{-1}.
Incidence = 1·85 + 0·171× 244 = 43·6 %

The 43.6 % is not far from 50 % where n = 8.

Therefore, until more data are available, I suggest the use of Eq. 12 for saturation diving at the lower range of toxic PO_2.

6. Recovery time constant

From the similar values of recovery time constants at saturation 0.0135 h^{-1} (PO_2 0.55 bar) to that at PO_2 of 1.05 bar, namely 0.0128 (Arieli et al., 2002) it may be suggested that the value of the recovery time constant levels off below PO_2 of 1.1 bar (Fig. 3).

7. Further research

Recently, earlier markers of POT have been presented in volatile organic compounds in the exhaled breath (de Jong et al., 2022b,a). It would be interesting to relate these markers to the POTindex, in an effort to predict the earliest signs of POT. Does the appearance of POT markers with specific POTindex are individual related or not? What is the relationship between early signs and a detected pulmonary toxicity manifestation?

8. Conclusions

The POTindex calculated by the power equation $K = t^2 \times PO_2^{4.57}$ with the recovery form $Ktr = Ke \times e^{\frac{1}{2x}[\text{illegible}]0.42 + 0.384 \times (PO}$ which are based on chemical and physiological principles, has a better prediction power than other suggested approaches. Both the cumulative pulmonary toxic effect and concomitant recovery are suggested to operate at the lower toxic range of PO_2: $K = t^2 \times PO_2^{4.57} \times e^{-0.0135 \times t}$ used in saturation diving. The superiority of the POTindex on other approaches, mainly UPTD, led many diving institutes to abandon UPTD for the POTindex (personal communications). Recently, the use of POTindex was recommended by experts in the field (Risberg and van Ooij, 2022; Salm, 2023).

Conflict of interests

The author declare that they have no conflict of interest.

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