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Hyperoxic exposure monitoring in diving: A farewell to the UPTD

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ABSTRACT

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Depending on pO_2 and exposure time hyperoxic breathing gas may cause injury in many organs including the lungs. Pulmonary oxygen toxicity (POT) may be asymptomatic, but will initially present as a tracheobronchitis in symptomatic subjects. A number of objective measurements of POT have been investigated, but the decrement in vital capacity (VC) has remained the most accepted outcome measure. The unit pulmonary toxic dose (UPTD) has been established as the most common exposure index for POT in diving. UPTD is calculated based on the pO_2 and exposure time. A literature search identified five models predicting POT, but no model would accurately predict VC change for the full range of pO_2 variation and exposure time relevant for surface-oriented diving. Nevertheless, compared to UPTD, the K-index ($K = t^{2}*pO_2^{4.57}$, where t = time (hours) and pO_2 = inspired pO_2 (atm)) suggested by Arieli performed better for pO_2 > 150 kPa and allowed estimation of recovery. We recommend that the Arieli K-index should replace UPTD as the POT exposure index for all surface-oriented diving. Based on the limited data available we suggest a daily threshold of K = 120 for a maximum of two diving days followed by two days of recovery. For five consecutive days of diving, we recommend that the threshold should not exceed K=70 and two recovery days should be allowed. For multiday diving without days of recovery, the daily exposure should probably be limited to K = 40-50. ∎

KEYWORDS: diving; oxygen; pulmonary function; pulmonary oxygen toxicity; UPTD

INTRODUCTION

Divers will normally breathe hyperoxic gas mixtures during diving: i.e., an inspiratory pO_2 (partial pressure of oxygen) that exceeds the normal atmospheric partial pressure of 21 kPa. Hyperoxia is known to have a toxic effect on a number of organ systems depending on pO_2 and exposure time [1]. The most extensive effects are those on the lungs and central nervous system (CNS). CNS toxicity will typically develop after minutes to a few hours of exposure to pO_2 exceeding 150-160 kPa. Pulmonary toxicity may develop after days of exposure exceeding 50 kPa but can also develop after hours of exposure if pO_2 exceeds 100 kPa.

Clinically acute pulmonary oxygen toxicity (POT) is recognized as a tracheobronchitis with cough, chest pain and dyspnea. However, these subjective symptoms may be difficult to identify in the early phase. Comprehensive reviews of POT have been published detailing the pathophysiology of the injury [2,3]. After initial airway irritation, hyperoxia will initially cause pulmonary interstitial edema and inflammation (i.e., the exudative phase). If hyperoxia is continued, this is followed by fibrosis and emphysema, or the proliferative phase. A large number of lung function parameters have been investigated in search of an objective and preferably presymptomatic measure of POT. Total lung capacity (TLC), forced vital capacity (FVC), forced

expiratory volume in the first second (FEV_1), mid-expiratory flow rates, indexes of pulmonary gas diffusion rates, concentration of volatile organic compounds and NO in expiratory gas are but a few of the parameters that may be affected in the short term by hyperoxic breathing gases. However, the reduction in vital capacity (VC) remains the best-studied outcome measure of POT caused by hyperbaric hyperoxia.

In addition to the short-term POT, hyperoxia may leave permanent pulmonary sequelae, though the extent of these changes is debated. Tetzlaff et al. [2] published a review on this question in 2017. A reduction of FVC, FEV_1 and flow rates in mid- and low lung volumes have been reported in many studies, while other studies were unable to identify any change. This may be explained partly by study design (cross-sectional or prospective) and inclusion criteria (commercial or naval divers, saturation or surface-oriented diving). However, the prospective studies generally conclude that the changes are of a small and clinically insignificant order.

Use of hyperoxic breathing gas during diving has obvious benefits. Increasing pO_2 will decrease the pN_2 (partial pressure of nitrogen) and thus allow a reduction in decompression time and/or reduction of decompression sickness incidence. In deep saturation diving the oxygen fraction may be in the order of 1% to 2%. A slight hyperoxia in the chamber and during lockouts from the bell provides protection from hypoxia in the event of erroneous gas measurements. The appropriate pO_2 for a dive should be balanced between the likelihood and extent of POT against a number of operational, technical and economic factors.

In 1970 Bardin and Lambertsen [4] introduced the unit pulmonary toxic dose (UPTD) as a POT exposure index. It is commonly referred to as oxygen toxicity unit (OTU) outside the scientific environment. The unit was defined as a one-minute exposure to pO_2 = 1 atm (101 kPa). A formula (Equation 1, presented later) allowed estimation of POT with any pO_2 or exposure time. Later works [5-7] have introduced alternative exposure indices. In spite of the fact that van Ooij et al. [3] claimed that an alternate index proposed by Arieli (the Arieli K-index) [8] "remains the most sophisticated VC-based model," the UPTD concept seems to remain "a gold standard" for occupational hygienic assessment of the hyperbaric hyperoxic exposure dose. Two of the most recent manuscripts [9,10] discussing POT in diving address the hyperoxic exposure by means of UPTD. Civilian [11] as well as military [12] decompression tables still advise to monitor the hyperoxic exposure by means of UPTD.

Shykoff [13] has published the most extensive review of models predicting VC changes during and after hyperoxic exposures. VC data were retrieved from 35 different experimental conditions and 351 subject exposures with exposure pO_2s ranging from 84 to 253 kPa (0.83 to 2.5 atm) and exposure time up to 72 hours. Nineteen individual models were tested against this data set. Observed changes in VC were compared to model estimates by means of non-linear regression. The author concluded that no universal model could appropriately describe changes in VC based on pO_2, exposure time and recovery time for the full dataset. Model performance varied dependent on pO_2, exposure time and intermittence of breathing the hyperoxic gas. Equally important, the large individual differences in response to hyperoxic exposure would restrict any model to describe about half of the total variability.

The Shykoff work [13] reviewed the full range of continuous and intermittent hyperoxic exposure data with pO_2 84 to 253 kPa lasting 0 to 72 hours available at that time. The objective of this study was limited to review proposed indexes of POT for exposures relevant for *manned, surface-oriented diving*. Surface-oriented diving is the most common type of occupational, military and recreational diving. The diver enters and exits the water to/from surface and is exposed for increased ambient pressure in the range of minutes to a few hours. Surface-oriented diving contrasts saturation diving in which the divers remain in a pressurized chamber complex for days and weeks and are transferred

to the worksite by a closed diving bell. The main question to be answered was whether other exposure indices than UPTD would better describe the development of POT. Exposure for hyperoxia relevant for hyperbaric oxygen treatment or saturation diving was considered outside the scope. Similarly, we consider the assessment of exposure indices for CNS oxygen toxicity outside the scope of this work. The authors completed this task in their position as members of The Diving Medical Advisory Committee (DMAC *www.dmac-diving.org*). DMAC is an independent body that provides advice about medical and certain safety aspects of commercial diving.

METHODS

A PubMed search with search term [pulmonary oxygen toxicity diving] was completed 17 February 2022. The titles and abstracts were reviewed by both authors. Full-text manuscripts were reviewed for studies investigating the relationship between pO_2 and hyperoxic breathing time on POT. Dry and immersed exposures were included as were normobaric and hyperbaric exposures. The references in these primary studies were reviewed, and any reference fulfilling the inclusion criteria was included.

Studies were included if they suggested indices for oxygen exposure intended to control POT in divers. Studies were rejected if they presented only models and formulas without suggested parameters for human hyperoxic exposure. Methods were reviewed based on the details of the dataset they were based on including the outcome variable chosen (pulmonary function, symptom), pO_2 range, immersion or dry exposure, and rest or working state. Pressure units are presented as published in the reports and converted to kPa according to the conversion factors printed in *U.S. Navy Diving Manual* Rev 7 [14]. Some studies have quoted partial pressure values in ATA (atmospheres absolute pressure), others with "atm." We have chosen to use the unit "atm" throughout.

Most included studies predicted POT by means of VC changes. We have compared the predicted VC changes to VC data from hyperoxic exposures ranging from 83 to 304 kPa [15-19]. The findings are presented in plots. We have had neither access to all original data (such as the extensive data set submitted to the U.S. Navy Experimental Diving Unit [20]) nor the capacity to complete the nonlinear regression analysis performed by Shykoff [13]. For this reason we will refer to her review when we report the statistical association between VC data and the various models. While Shykoff [13] modified the formulas and parameters of the various models to optimize prediction of VC change, we have used the formulas and parameters as presented in the original works (see "Model Descriptions" below).

RESULTS

The PubMed search retrieved 84 results. The abstracts of these were reviewed. Five of them fulfilled the inclusion criteria for POT exposure indices [5,6,8,21,22]. These five reports were reviewed in full text. One additional study by Vann and a review by Shykoff were included [7,13] as a result of this initial review. Three of the studies [6,8,21] discussed the same model. A summary of the four models is presented in Table 1. The details of each model are presented below.

MODEL DESCRIPTIONS

Bardin and Lambertsen UPTD

The UPTD concept was first published in a report in 1970 by Bardin and Lambertsen [4]. Their work was based on the seminal thesis of Clark and Lambertsen [16] published the same year. Clark and Lambertsen [16] reanalyzed an earlier work by Marshall and Lambertsen [23] observing lethality in mice exposed to hyperoxia. Mortality could be modeled by a rectangular hyperbolic relationship of pO_2 and exposure time. In the thesis [16] they reported changes in VC on 11 resting subjects breathing 100% O_2 in the pressure chamber at 2 atm (203 kPa) for nine to 12 hours. These data were supplemented by findings from two previous studies [15,19] measuring pulmonary function after prolonged hyperoxic exposure to pO_2 = 0.83 atm (84 kPa, N = 6) and pO_2 = 0.98 atm (99 kPa, N = 4). Clark and Lambertsen [16] plotted VC

Table 1 : Summary of studies suggesting exposure indices relevant for monitoring pulmonary oxygen toxicity in divers

index proposed	originally included	exposures	pO_2 range (kPa)	relationship between pO_2 & time vs VC change	outcome measure	recovery function	comment
UPTD	Bardin & Lambertsen 1970 [4]	21	84-203	(rectangular hyperbola)	(VC)		Relationship between pO_2 & time expressed as UPTD (rectangular hyperbola). Relationship between UPTD & VC was not mathematically expressed but tabulated.
unnamed	Harabin 1985 [22]	440	25-203	linear	VC		
Repex	Hamilton et al. [24]				(VC)	+	The Repex report holds recommendations for limiting UPTDs for multiday exposure, i.e. inherent expectations of POT recovery
FR(1)-VC(2) FR(2)-VC(2)	Vann 1988 [7]	794	25-203	exponential	VC	+	
Arieli K	Arieli et al. 2002 [8]	56	106-304	exposure: power recovery: exponential	VC	+	
ROT	Shykoff 2015 [5]	1352	130-140	exposure: exponential recovery: sigmoidal	FVC, FEV_1, $FEF_{25-75\%}$ or pulmonary symptoms	+	POT expressed as a likelihood function

Summary of indices proposed for oxygen exposure monitoring in relation to pulmonary oxygen toxicity
ROT: residual oxygen time VC: vital capacity other abbreviations: see text.

isopleths for pO_2 and time combinations by best fit between these points. Bardin and Lambertsen [4] introduced the mathematical relationship of UPTD by the now well recognized Equation 1.

$$UPTD = t \cdot \sqrt[-1.2]{\frac{0.5}{pO_2 - 0.5}}$$

Equation 1. *UPTD as a function of exposure time (t, in minutes) and pO_2 (atm). From [4].*

Each UPTD isopleth will be described by a rectangular hyperbola of pO_2 and exposure time. The authors published a table (Table 2) relating seven UPTDs to median VC reduction. In the present work we have applied linear interpolation to estimate VC changes for exposures ranging from 615 to 2,190 UPTD.

Hamilton et al. (Repex)

The Repex report [24] holds recommendations for limiting oxygen exposure for multiday diving.

Table 2

UPTD	ΔVC (%)
615	-2
825	-4
1035	-6
1230	-8
1425	-10
1815	-15
2190	-20

Relationship between UPTD dose (see text) and median vital capacity (VC) reduction as originally published [4].

The recommended UPTD limit was dependent on the number of diving days (Table 3). The limits were based on "expert opinion" rather than statistical analysis of data. The Repex table could be considered to hold expectations of POT development related to exposure as well as recovery.

Table 3

exposure (days)	avg daily dose (UPTD)	exposure (days)	avg daily dose (UPTD)
1	850	7	380
2	700	8	350
3	620	9	330
4	525	10	310
5	460	>10	300
6	420		

Exposure limits (UPTDs - see text) for hyperoxic exposure depending on number of days of exposure. From [24].

Harabin et al. (VC)

Harabin et al. [22] analyzed a dataset from 13 studies reporting VC changes in 440 subject-exposures to hyperoxia ranging from pO_2 = 0.25-2.0 atm (25-203 kPa). The data was analyzed by a non-linear least square error analysis for a best fit to the following general equation:

$$\Delta VC = B_S \cdot (pO_2 - B_1) \cdot (t - B_2)^{B_3}$$

▲ ***Equation 2.*** *Generic equation suggested by Harabin et al. [22] for calculating the reduction in VC as a function of pO_2 (atm) and exposure time (t(min)). B_S, B_1, B_2 and B_3 are constants related to the slope, pO_2 asymptote, time asymptote and exponent respectively.*

Best fit was reached by fitting B_S = -0.009, B_1 = 0.38, B_2 = 0 and B_3 = 1 allowing a simplification according to Equation 3 below.

$$\Delta VC = B_S \cdot (pO_2 - B_1) \cdot t$$

Equation 3. *Best fit equation for reduction of VC (% change) after hyperoxic exposures as reported by Harabin et al. [22]. pO_2 in atm and time (t) in minutes.*

However, the authors concluded that maintaining the pO_2 asymptote (B_1) at 0.5 atm (51 kPa) as suggested by Bardin and Lambertsen [4] would affect VC estimation with <1% if B_S was adjusted to -0.011. We have applied the latter parameters in our comparison. As can be seen, the predicted VC reduction is a linear function of pO_2 and time. This model was classed as a "proportional model" class by Shykoff [13].

Vann (FR(1)-VC(2) and FR(2)-VC(2))

In this work [7] the author used VC change as the outcome measure of POT. He fitted the same data set used by Harabin et al. [22] but included additional control measurements, thus reaching a total of 794 VC measurements. VC measurements during and after hyperoxia were expressed as relative values of the pre-exposure measurement – i.e., using 100% as the baseline measurement for each individual. An equation based on a "free radical model" (FR model) was used to express the mass balance of production and removal of a toxic substance (e.g., reactive oxygen species (ROS)). The presumption was that VC reduction would be proportional to the concentration of this toxic substance. Two equations for the production of the toxic substance were suggested (termed FR(1) and FR(2)). The important difference from the equation suggested by Harabin et al. [22] was that FR(2) allowed consideration of elimination of the toxic substance. The relationship between the concentration of the toxic substance (F) and VC reduction ▶

was expressed with two equations (VC(1) and VC(2)). The simplest FR(1)-VC(1) suggested a linear relationship between pO_2 and exposure time on VC. This model was classed as a "proportional model" by Shykoff [13]. The best fit equation (termed FR(2)-VC(2) by Vann, presented as Equation 4 below), was rather complex, but allowed estimation of POT recovery, thus estimating the effects of varying pO_2s and repeated exposures. This model was classed as "proportional rate of healing" by Shykoff [13].

$$F(t) = (F_0 - k) \cdot e^{-2.8 \cdot 10^{-8} \cdot t} + k \text{ where } k = \frac{0.021 \cdot pO_2 - 8.61 \cdot 10^{-3}}{2.8 \cdot 10^{-8}}$$

$$\Delta VC = -100 \cdot (1 - 1.0055^{-F})$$

Equation 4. *Toxic index (F) as a function of pO_2 (atm) and time (t (min)) including relationship to vital capacity reduction (ΔVC) according to the Vann FR(2)-VC(2) equation [7].*

However, the simpler FR(1)-VC(2) model (Equation 5 below) showed only a slightly inferior performance for single exposures to a constant pO_2. The best fit parameters to the FR(1)-VC(2) equation are shown in Equation 5 below.

$$\Delta VC = -100 \cdot (1 - 1.0055^{(0.021 \cdot pO_2 - 0.00861) \cdot t})$$

Equation 5. *Best fit equation for the effect of hyperoxic exposure on VC (% change) as suggested by Vann [7]. pO_2 in atm and time (t) in minutes. The author provided only one example of prediction performance of recovery function of the FR(2)-VC(2) model.*

Arieli [8] (Arieli K)

Arieli [8] used the index "K" to express "an oxygen-damaged measurable physiological variable." To facilitate recognition of the index we have termed it "Arieli K" in this work. The theoretical basis was the presumption that an "oxygen-damaged measurable physiological variable (DMG)" would have the same relationship to exposure time and pO_2 as the reactive oxygen species that caused the damage [6]. Recovery would take place when pO_2 was decreased below the threshold needed to develop DMG. Earlier works by the same author [6,25] suggested that the production of ROS would be a power function of time as well as pO_2. Arieli [8] fitted VC measurements from three earlier studies with pO_2 ranging 1-3.5 atm (101 to 355 kPa) [17,18,26] to a power equation and suggested parameters as presented in Equation 6.

$$\Delta VC = 0.0082 \cdot t^2 \cdot pO_2^{4.57}$$

Equation 6. *Best fit equation for the effect of hyperoxic exposure on VC (% change) as suggested by Arieli et al. [8]. Exposure time (t) in hours and pO_2 in atm.*

The authors suggested that POT alternatively could be expressed by a "K" index simply by removing the constant from Equation 6 above. The Arieli K-index would thus be calculated such:

$$K = t^2 \cdot pO_2^{4.57}$$

Equation 7. *The Arieli K-index (K) expressed as a function of exposure time (t in hours) and pO_2 (in atm). From Arieli et al. [8].*

The Arieli K-index could be considered as an alternative to the traditional UPTD. For an exposure with discrete elements (i = 1 to n) with a constant pO_{2i} for a time (t_i) for each segment, the K-index should be calculated such:

$$K = \left[\sum_{i=1}^{n} t_i \times pO_{2_i}^{2.285}\right]^2$$

Equation 8. *The Arieli K-Index (K) for a sequence (i = 1 to n) of hyperoxic segments with individual exposure times (t (hours)) and pO_2 (atm).*

Recovery was expressed by Equation 9 below.

$$\Delta VC_r = \Delta VC_e \cdot e^{(0.42 - 0.384 \cdot pO_2) \cdot t}$$

Equation 9. *Best fit equation for the recovery of VC (ΔVC_r) after a hyperoxic exposure as suggested by Arieli et al. [8]. ΔVC_e: Reduction in VC after the hyperoxic exposure; pO_2: pO_2 (atm) during the hyperoxic exposure; t: recovery time (h) in normoxia. The same equation can be expressed to calculate the reduction in K during normoxic breathing by replacing ΔVC_e with K present immediately after the first hyperoxic exposure.*

The Arieli K was classed as an "exponential model" by Shykoff [13] (though strictly it is a power function).

The time constant for recovery was originally fitted for exposures with pO_2 exceeding 111 kPa. In a later work [21] the author has suggested a modified equation for calculating the K-index in saturation diving with continuous exposure to pO_2 <<111 kPa. However, the estimation of POT in saturation diving is beyond the scope of this work.

It should be noted that Arieli [8] determined the parameters based on mean changes in VC in contrast to Harabin [22] and Vann [7], both of whom used the individual VC measurements.

Shykoff (residual oxygen time)

This [5] is the most recent and most sophisticated model for predicting POT. The author analyzed 1,352 man-dives with pO_2 ranging from approximately 130 to 140 kPa. The database included exposures up to eight hours and surface intervals ranging from two to 20 hours for repeated dives. Dry and wet exposures with both resting and exercising divers were included in the analysis. The outcome measure was the presence of any recognized symptom of pulmonary oxygen toxicity or a change in any of three defined spirometric indices exceeding expected variation. The spirometric indices included forced vital capacity (FVC), forced expiratory volume in one second (FEV_1) and forced expiratory flow from 25% to 75% of vital capacity ($FEF_{25-75\%}$). Based on the institutional experience of intraindividual variation in these parameters, a decrement of either FVC > 7.7%, FEV_1 > 8.4 % or $FEF_{25-75\%}$ >17% would qualify for the assumption of POT. The outcome was thus a binary outcome of either symptoms or findings of POT. The likelihood of POT was analyzed by logistic regression. The result was presented as a probabilistic expression with parameters shown in Equation 10 below:

$$P_{POT} = \frac{100}{(1 + e^{\,3.586\text{-}0.49 \cdot t})}$$

Equation 10. *Probability (%) of POT (P_{POT}) for dives with pO_2 ranging from 130 to 140 kPa depending on exposure time (t in minutes) as suggested by Shykoff [5].*

Recovery was modeled according to Equation 11 below. Recovery from POT was expected to start five hours after the completed dive. Exposure times for dives with shorter surface intervals could be added to estimate the POT. The author introduced the term "residual oxygen time" to indicate the likelihood of persisting POT symptoms or spirometric changes after a surface interval. The residual oxygen time would be the exposure time to pO_2 130 kPa required for a previously unexposed subject to achieve a likelihood of POT similar to that of a subject recovered after a given surface interval. The residual oxygen time was expressed as shown in Equation 11 below.

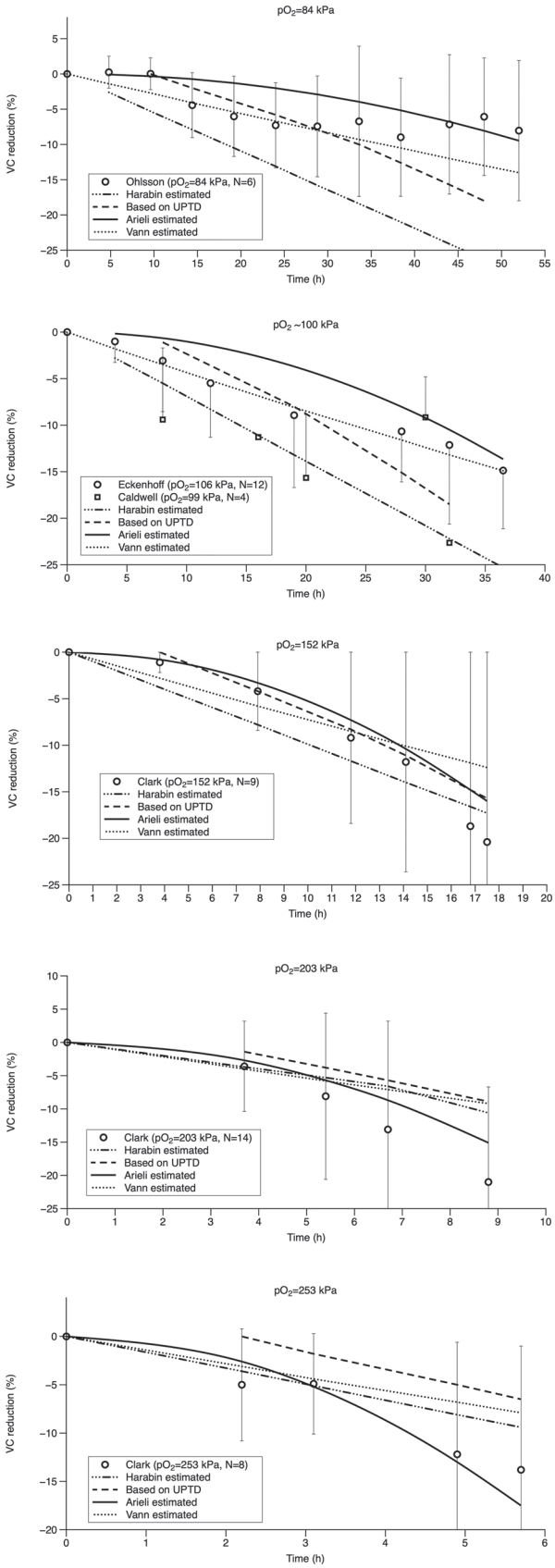
$$t_r = t \cdot e^{k \cdot (\frac{t_{SI}-5}{t})^2}$$

Equation 11. *Residual oxygen time (tr, see text) after a hyperoxic exposure to 130-140 kPa for time t after a surface interval of tSI. All times to be expressed in h. The constant k is -0.149 for resting divers and -0.047 for exercising divers. Equation as published by Shykoff [5].*

MODEL COMPARISON

Exposure

The shape of the dose-response curve of VC reduction during hyperoxic breathing is dependent on pO_2 as discussed in detail by Shykoff [13]. As can be seen from Figure 1, upper two panels, VC is hardly changed during the first five hours of exposure to pO_2, ranging from 84 to 106 kPa. For longer exposures the VC reduction is almost linear with time, or slightly curvilinear concave upward. It should be noted that the work of Caldwell [19] included only four subjects; the results were biased, as subjects were gradually excluded for exposure time exceeding 30 hours, and measurements were not completed at the same time in all subjects. For exposures to relatively low pO_2 and for exposures exceeding five hours it can be seen (Figure 1, upper two panels) that UPTD will underestimate the POT of short exposures and overestimate the effect of long exposures. The Vann [7] VC estimate serves



comparatively well for most of the exposure range while the Harabin [22] VC estimate generally overestimates the POT. The Arieli K [8] consistently underestimates the effect of this range of hyperoxia on VC.

Two important studies have reported POT after hyperoxic exposures ranging from 130 to 150 kPa [5,18]. The study by Clark et al. [18] reported VC changes during 17.5 hours of continuous exposure to 152 kPa (1.5 atm). For exposures up to 14 hours both UPTD and Arieli K will serve well to predict development of VC reduction (Figure 1, middle panel). The Vann [7] prediction will overestimate the POT of short exposure times and will underestimate the effect of longer exposure times. The Harabin et al. [22] VC prediction consistently overestimates the VC reduction to this pO_2 exposure level. The study by Shykoff [5] included 1,352 mandives with pO_2 ranging from 130 to 140 kPa and various combinations of exposure and recovery times. The POT incidence plot (Figure 2) shows a sigmoidal shape in agreement with Equation 10. The probability of POT (P_{POT}) estimated by Shykoff [5] compares well to the VC reduction predicted by Arieli K (Figure 2 upper panel). The upper panel shows that the incidence of symptoms and findings of POT at 130 to 140 kPa compares closely to the reduction in VC as predicted by Arieli [8]. In contrast, neither the VC predictions of Bardin and Lambertsen [4], Vann [7] or Harabin et al. [22] show dose-response curve similar to P_{POT} at this level of pO_2.

For pO_2 ranging 203 to 253 kPa (2.0 to 2.5 atm, Figure 1, lower two panels) the observed VC reduction is predicted reasonably well by all of the suggested equations for short and moderate length exposures. For long exposures, VC reduction is

Figure 1. *Observed reduction in vital capacity (VC) after hyperoxic exposure to 0.83; 1, 1.5; 2.0 and 2.5 atm (84, 152, 203 and 253 kPa) [15,18,19,26] compared to predictions [4,7,8, 22]. Observed changes presented as mean ± SD. For the work of Caldwell [19] SD is omitted for the three VC measurements for which only one subject was measured.*

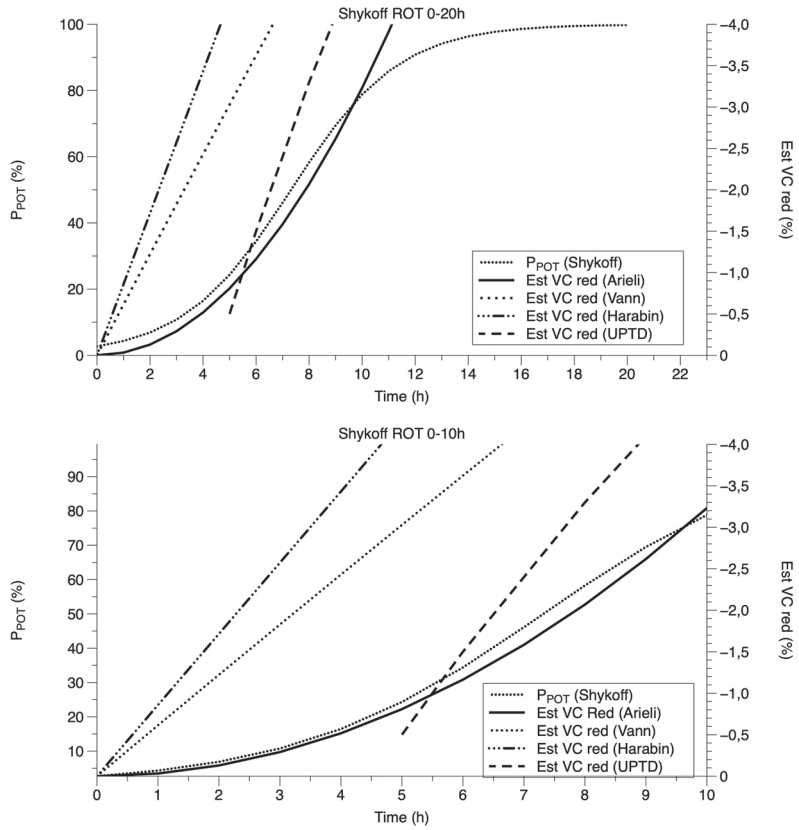


Figure 2. *Probability of POT (P_{POT}) as a function of exposure time to pO_2 130 to 140 kPa according to Shykoff [5] (left axis). VC reduction as predicted by Arieli [8], Bardin and Lambertsen [4]; Harabin et al. [22] is shown on the right axis. Upper panel exposure time 0 to 20 hours; lower panel 0 to 10 hours of exposure time.*

significantly underpredicted based by the UPTD estimate [4], Vann [7] or Harabin et al. [22]. However, the Arieli K index performs well across all exposure lengths. Yet, even Arieli K underpredicted the VC decrements for long exposure to 203 kPa, as observed in the study by Clark et al. [18] (Figure 1).

Lambertsen and Clark [27] have reported lung function changes during intermittent oxygen breathing at 203 kPa (2 atm). Subjects breathed 100% O_2 for 60 minutes followed by 15 minutes of compressed air ("air break") (N = 7) or 30 minutes of O_2 followed by a 30-minute air break (N = 6). These cycles were repeated for an accumulated oxygen breathing time of 14 hours unless excessive symptoms appeared, or VC reduction exceeded 20%. A similar study was completed by Hendricks [28] alternating 20 minutes of O_2 breathing and five-minute air breaks at 203 kPa. The findings are summarized in Figure 3 and show that none of the estimates fitted the observed findings. It is particularly striking that a 20:5 O_2: air breathing pattern at 203 kPa can be extended for 11 hours of oxygen breathing (almost 14 hours of total exposure time) with a modest reduction in VC of 2.8%. Data thus suggests that any of the established indices will overestimate the POT of intermittent oxygen breathing relevant for in-water and closed-bell decompression.

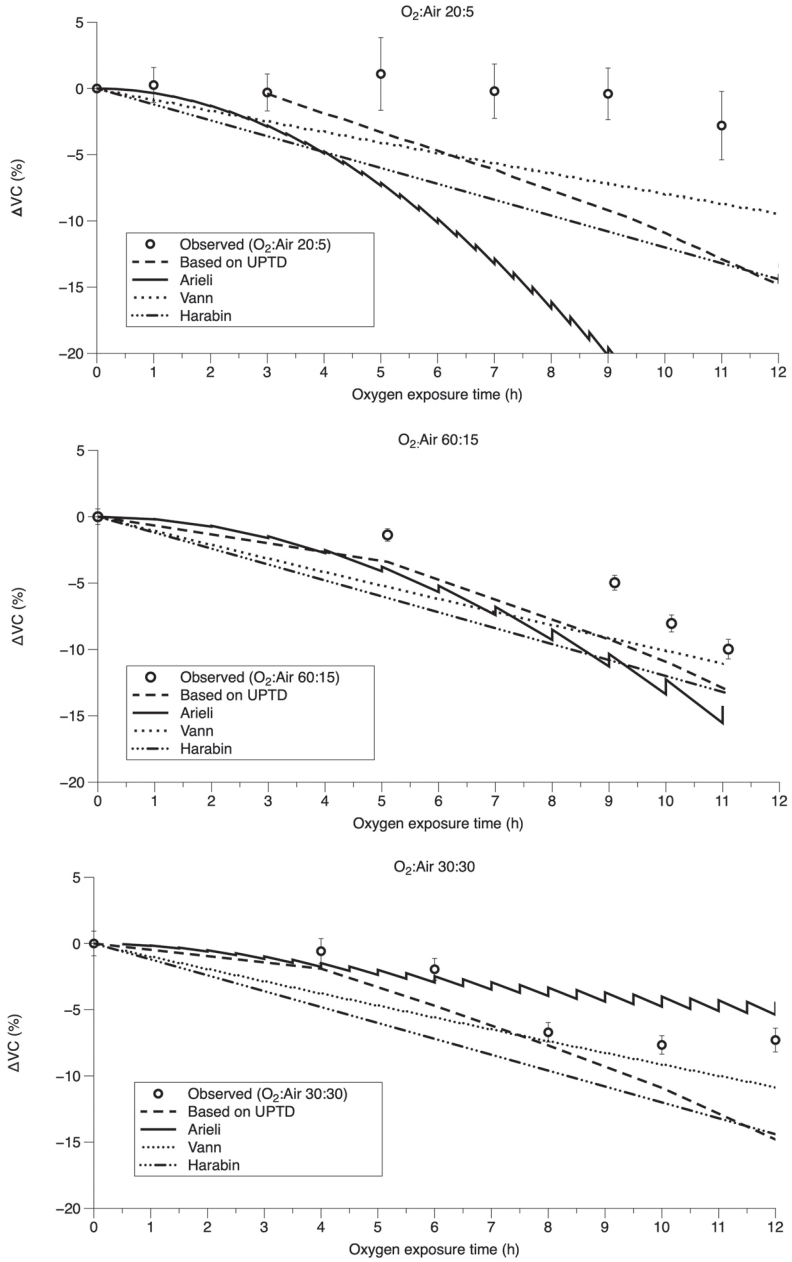


Figure 3. *Reduction in vital capacity (ΔVC(%)) during intermittent breathing of 100% oxygen and compressed air at 203 kPa (2 ATA) as reported by Hendricks et al [28] (top panel) and Lambertsen and Clark [27] (lower two panels). Oxygen : compressed-air intervals (min): Top panel 20:5 (N=5); middle panel 60:15 (N=7); lower panel 30:30 (N=6).*

Recovery

Recovery of VC after exposure to constant pO_2 of 152, 203 and 253 kPa has been reported by Clark et al. [18] and is presented in Figure 4. As can be seen, there is close agreement between the actual observations and predictions based on Arieli K. However, the recovery based on Shykoff residual oxygen time [5] (Figure 5) for exposures ranging from pO_2 130 to 140 kPa does not agree well with either Arieli K or Vann [7]. This is as expected since the recovery function of the Shykoff residual oxygen time [5] is

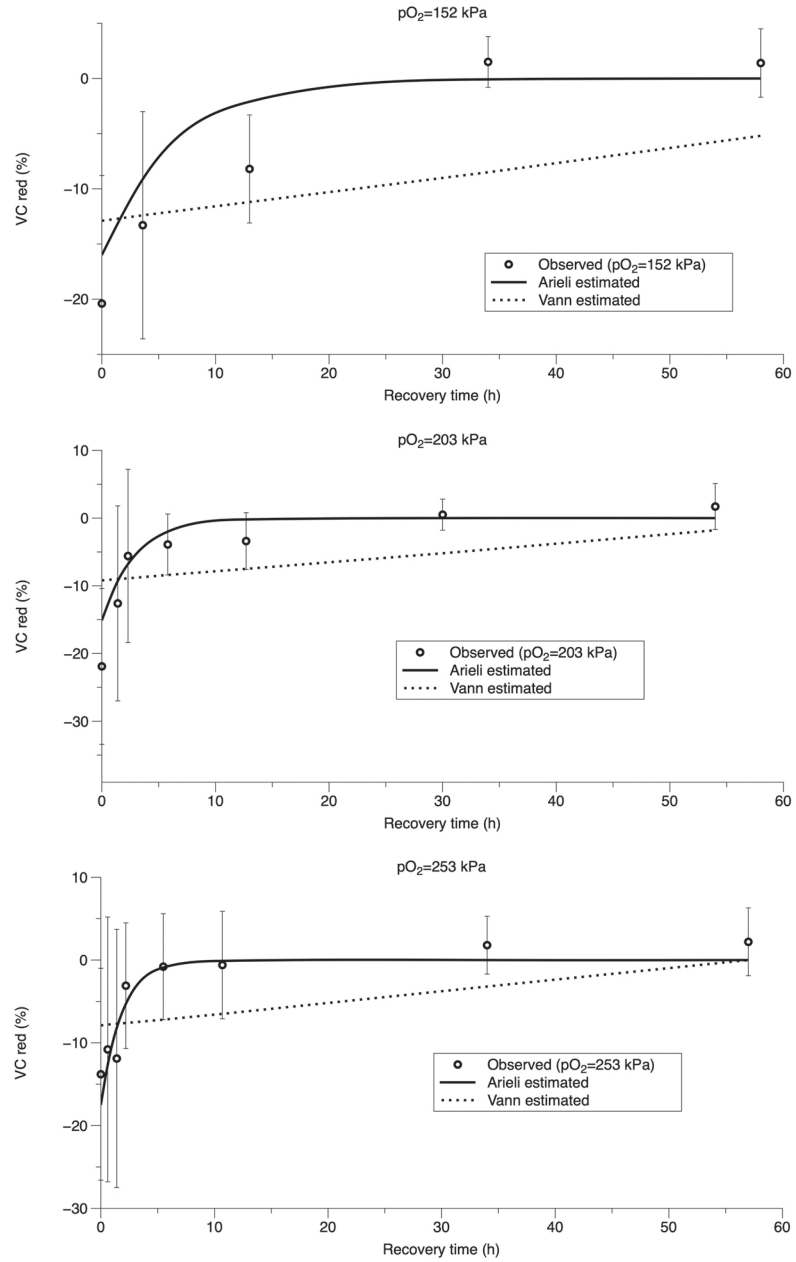


Figure 4. *VC recovery (% change from pre-exposure level) after 17.5-, 8.8- and 5.7-hour exposures to 152, 203 and 253 kPa as reported by Clark et al. [18], presented as mean ± SD. Recovery at normobaric normoxia (x-axis). Predictions of recovery suggested by Vann [7] and Arieli [8] shown as dotted and solid lines, respectively.*

fundamentally different from the two other concepts proposed [7,8]. Shykoff assumed recovery to take place exponentially after a five-hour delay at the surface, while no such delay is implied in the Arieli and Vann equations. The UPTD concept does not allow estimation of recovery.

DISCUSSION

The ideal exposure index would allow estimation of the incidence, severity and development of symptoms and findings of POT across various exposure levels and exposure times. No such exposure index is presently available. Pulmonary symptoms

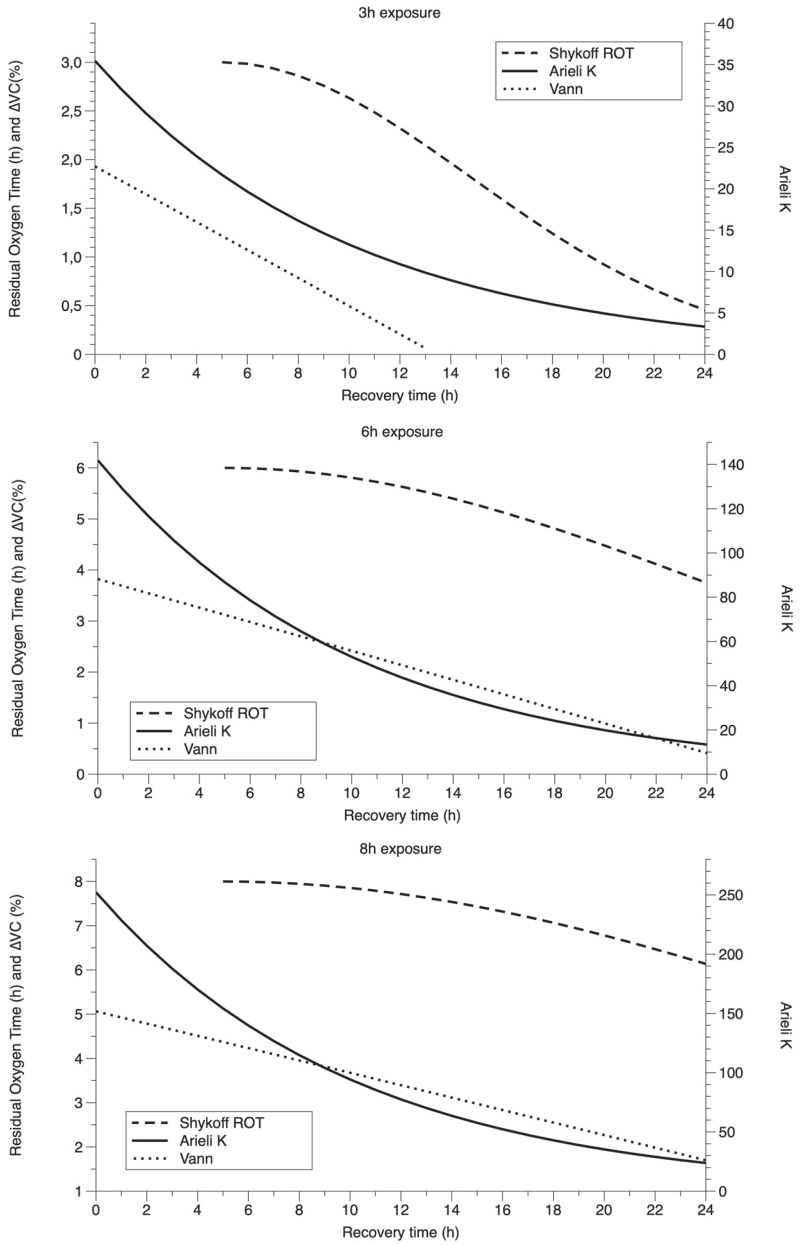


Figure 5. *Recovery from 3-, 6- and 8-hour exposures to 130 to 140 kPa expressed as "residual oxygen time" (ROT) (left axis) according to Shykoff [5]. Recovery of Arieli K (right axis [21]) and ΔVC (left axis) as predicted by Vann [7].*

may precede changes in pulmonary function, but symptoms and findings develop differently between individuals, and symptoms are difficult to quantify. Reduction in pulmonary diffusion capacity (DLCO) probably takes place before other spirometric indices are affected [3]. However no other spirometric index has been studied as extensively across a broad range of pO_2 and exposure times as VC. Our expectation is that a model that would predict changes in VC could be used as a reliable measure of POT. Establishing an appropriate threshold for VC reduction is expected to limit other effects of POT as well such as symptoms and pulmonary function.

Table 4. Extract from Table 4 in the Shykoff report [13]

Model	Cont. Exp.		Cont. + Intermitt. Exp.	
	E	E+R	E	E+R
UPTD [4]	35 %		32 %	
proportional [7,22]	35 %	33 %	33 %	33 %
proportional healing [7]	75 %	60 %	71 %	56 %
exponential [8]	66 %	61 %	25 %	53 %

Performance of four of the models expressed as percentage of (r^2 of model)/(r^2 of intersubject average for the dataset). A high number indicates that the model can describe most of the change not related to intersubject variation.
Cont. Exp = Continuous exposure; Cont. + Intermitt. Exp. = Continuous exposures and exposures with intermittent "air breaks" (see text).
E: Performance of hyperoxic exposure only.
E+R: Performance of hyperoxic exposure as well as recovery.

Shykoff [13] has published the most extensive review of models predicting VC changes during and after hyperoxic exposures. VC data were retrieved from 35 different experimental conditions and 351 subject exposures with exposure pO_2s ranging from 84 to 253 kPa (0.83-2.5 atm) and exposure time up to 72 hours. No immersed exposures were included. Some of the experimental conditions were similar and were grouped to facilitate data interpretation. Nineteen individual models were tested against this data set. Some models were based on the same principle and were grouped together in nine major classes. Five classes of models had been published earlier [7,16,22,25,29], while four additional models were proposed and tested by the author. Observed changes in VC were compared to model estimates by means of nonlinear regression and model performance reported as regression coefficients (r^2) for most datasets. Performance was investigated for the immediate pulmonary insult as well as the recovery process. The author concluded that no universal model could appropriately describe changes in VC based on pO_2, exposure time and recovery time for the full dataset. Model performance varied dependent on pO_2, exposure time and intermittence of hyperoxic breathing ("air breaks"). Equally important, the large individual differences in response to hyperoxic exposure would restrict any model to describe about half of the total variability. This is in agreement with previous reports [16,22] and should be considered when any model is applied to predict POT after hyperoxic exposures. Experimental studies on rats suggest that the mechanism of POT differ depending on whether the animal is exposed to a long-lasting exposure to moderate hyperoxia (pO_2 = 101 kPa for 56 hours) or short-lasting exposure to high pO_2 (pO_2 = 304 kPa for six hours) [30]. This may explain why it is difficult to identify a single hyperoxic exposure index useful for all ranges of pO_2 and exposure times.

Shykoff [13] compared model performance by r^2 of model/r^2 of intersubject average (Table 4). The UPTD model by its original description showed performance ranging from 32% to 38%. The Arieli K index ranged 66% to 76% for continuous exposure but degraded to 25% when intermittent exposures were included. For recovery data, the Arieli K-index ranged 53% to 74% depending on exposure grouping. UPTD does not prescribe recovery after hyperoxic exposure. It should be noted that Shykoff adjusted the coefficients in these models by means of non-linear regression. The numbers presented in Table 4 should be considered as the performance of the model class with optimized parameters rather than the performance of the specific equations as published in the original reports [4,7,8,22].

The statistical analysis by Shykoff [13] agrees with the qualitative comparisons of the present study. This is expected since both studies share models and part of the dataset.

The purpose of this study was to investigate whether UPTD should be replaced as an exposure index for the hyperoxic exposure relevant in surface-oriented diving. The scope was thus narrower than that undertaken by Shykoff [13]. Most surface-oriented diving will take place using air as the breathing gas to depths not exceeding 50 meters of seawater (msw). Within this range the distribution of diving depths and bottom times will depend on the group being studied (recreational, occupational, military). When air is used as the breathing gas throughout the dive, only very shallow dives will allow exposures in the order of many hours without undue long decompression times. For instance, the bottom time for a dive to 18 msw (60 fsw) should be restricted to 120 minutes with air as a breathing gas during in-water staged decompression [14]. At this depth (pO_2 = 59kPa) and exposure time, no POT would be expected. Even in multiday diving with nitrox with pO_2 = 130 to 140 kPa in the bottom gas, the POT would be limited if the dive is restricted to four hours/day [31]. There are clearly accumulating effects of POT, and a six-hour multiday-exposure to pO_2 = 130 kPa causes a high incidence of POT symptoms and findings [32]. Though the works by Shykoff [5,32,33] provide a solid foundation for "single-level" hyperoxic exposure to 130 to 140 kPa dives – relevant for military diving – these data are less applicable for recreational and occupational surface-oriented diving. The military diver using a rebreather with constant pO_2 (an electronically controlled closed-circuit rebreather, or ECCR) will typically breathe through the rebreather throughout the dive without change of breathing gas pO_2 during decompression. In contrast, a recreational diver breathing from an ECCR may restrict bottom-phase pO_2 to a narrow range, typically 130 to 140 kP, but raise pO_2 during decompression – typically to 150 to 160 kPa. In occupational diving closed-bell decompression (TUP) will include breathing gases with pO_2 160 and 190 kPa. Surface decompression with oxygen will require the diver to breathe oxygen at 250 and 220 kPa. TUP and surface decompression with oxygen will typically include air breaks for every 20 to 30 minutes of oxygen breathing. There is an operational need to quantify POT after exposures to such complex hyperoxic exposures.

The UK Health and Safety Executive (HSE) has put in place bottom time limitation on surface-oriented diving applicable for UK commercial diving [34]. These limitations were later implemented in Norwegian regulations as well as dive manuals for a number of international diving contractors. The UK HSE bottom time limitations decrease allowed bottom time from four hours (at depths not exceeding 12 msw) to 20 minutes (at a depth of 51 msw). There is no limitation on decompression time, and if decompression takes place in a closed bell or chamber ("transfer under pressure") the allowed bottom time for any depth will be longer than if diving takes place with in-water staged decompression or surface decompression with oxygen. The highest POT burden for commercial surface-oriented dives respecting HSE bottom time limitation, decompressing according to USN [14], would be the dive presented in Figure 6. This is a dive to 30 msw with 33% oxygen, balance nitrogen, as the breathing gas. This will give a pO_2 = 132 kPa (1.3 atm) and an equivalent air depth of 24 msw. UK HSE regulations [34] will restrict bottom time to 180 minutes at this depth. In-water or closed bell decompression with oxygen would require 17 minutes of O_2 breathing at 9 msw (190 kPa) and 96 minutes at 6 msw (160 kPa). What would be the risk for POT if this was a single exposure or alternatively took place as multiday diving? Each dive would represent 495 UPTD (OTUs), and the Repex guidelines suggest a maximum of four successive days of diving with this level of hyperoxia. The Arieli K of this exposure would be 123. The bottom phase with pO_2 = 131 kPa would have a 10.8% likelihood of symptoms or pulmonary function changes according to the ROT model [5],

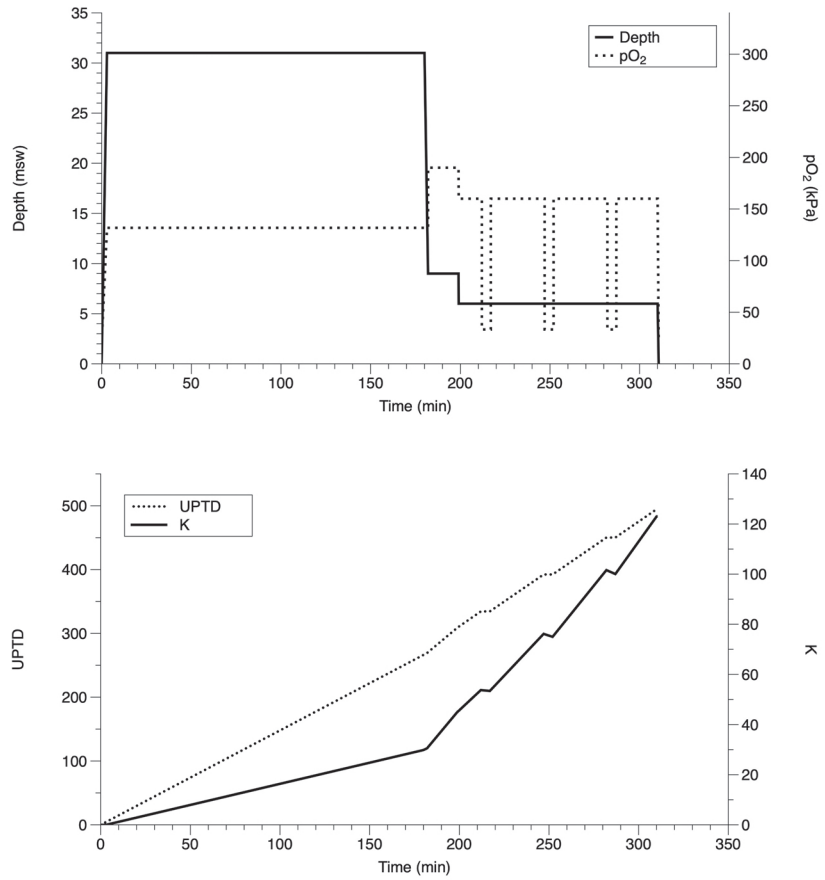


Figure 6. Depth and pO_2 profile (upper panel) and estimated POT (lower panel) during a dive to 31 msw breathing Nitrox with pO_2=132 kPa in the bottom phase. Intermittent breathing of 100% O_2 and compressed air at 9 and 6 msw. Profile according to USN Diving Manual Rev 7[14].

but the model will not be able to account for the succeeding hyperoxic exposure during decompression. The pulmonary effect of such a complex pattern of hyperoxia as illustrated in Figure 6 has not been tested experimentally. Any presumptions must be made based on the findings observed during a constant level of hyperoxia without intermittent "air breaks." The Shykoff [5] ROT model cannot be extended beyond the bottom phase. The almost linear development of POT suggested by the UPTD curve during the 131-kPa period (Figure 6) compares reasonably well to previous studies on pO_2 = 100 and 150 kPa (Figure 1). However, data suggest a more profound effect on VC as pO_2 raises beyond 150 kPa or exposure times are very long (Figure 1). The increase in Arieli K during the last part of the dive fit better to VC measurements achieved during exposures to pO_2 = 150 to 200 kPa (Figure 1). However, the intermittent five-minute air breaks at 6 msw would be expected to attenuate the POT during decompression (Figure 3).

There is insufficient scientific data to support any presumption of the development of POT during a multisegment hyperoxic exposure such as that illustrated in Figure 6. Table 5 gives a rough idea of the performance of UPTD and Arieli K used

Table 5. Comparison of fitness of UPTD and K to estimated decrement in vital capacity (VC) depending on pO_2 range and exposure time

exposure	pO_2 (kPa)	time (h)	time:VC relationship	estimate precision UPTD	K
continuous	<100	<5 h	0	–	–
continuous	<100	>5 h	Lin	↑	↑
continuous	130-140	0-10 h	Exp*	↑	–
continuous	150	0-10 h	Exp	–	–
continuous	200-250	0-5 h	Exp	↓	–
intermittent	200	0-4 h	0	↑	↑
recovery	150-250	0-24 h	Sigm or Exp		–

The column "Time:VC relationship" describes the relationship between VC reduction and exposure time for a given pO_2. (0 = No change; Lin =Linear; Exp = Exponential; Sigm = Sigmoidal). The estimate precision is presented as either fitting to data (–), overestimation (↑) or underestimation (↓). The table holds the interpretation of the data presented in Figure 1-Figure 4. *: The 130-140 kPa row summarizes the relationship between symptoms or findings of POT (not VC) and exposure time as reported by Shykoff [5].

as indices of POT caused by a exposure to a constant pO_2. The table summarizes the findings in the present work as well as the Shykoff study [13]. Even this overview has significant shortcomings beyond the obvious fact that it does not hold data for multilevel exposures. First of all, it depends on VC as a reliable measure of POT. As has been shown by others, pulmonary diffusion capacity and changes in expired NO and volatile organic compounds may precede changes in VC [3], but the changes in these parameters have not been studied to an extent allowing them to replace VC as the outcome measure. Secondly, and a more difficult question to resolve, is the fact that most studies of VC change have been made in resting divers during a single hyperoxic exposure in a dry chamber. A number of studies by Shykoff [30,32,35] are exemptions from this statement. The data from the Shykoff studies show that though the incidence of symptoms after a single hyperoxic exposure is small, the incidence raises during the course of a multiday exposure series. Further, the POT incidence is significantly higher in exercising compared to resting divers [32]. The findings call for caution when establishing exposure limits for occupational divers planning multiday diving with hyperoxic breathing gas.

In the absence of experimental data, arguments could be used to defend UPTD as well as Arieli K to express the POT of a complex dive as the one presented in Figure 6. Using the Arieli K would be a conservative approach as it will suggest that the POT acquired during the bottom phase would be augmented by hyperoxic breathing during decompression. In the absence of data it seems valid, based on the precautionary principle [36], to apply the most conservative method. Another important reason to prefer Arieli K to UPTD is that Arieli K allows estimation of recovery. Arieli K recovery function fits well to that observed after continuous exposure across a broad range of hyperoxia (Figure 4).

The Repex guideline would allow 850 UPTD for a single exposure. Though original sources are lacking, both Harabin and Arieli [8,22] claim that a 2% reduction in VC was a threshold established for U.S. Navy. This VC reduction would be expected

to be reached with 615 UPTD or K=244. It could be questioned whether 615 UPTD or K=244 is still too high – at least with a 130 to 140 kPa hyperoxic exposure burden. A threshold of 615 UPTD or K = 244 would be reached after 6:36 and 7:53 respectively breathing pO_2 = 135 kPa . This would be expected to cause POT symptoms (tracheobronchitis) or findings (spirometric changes) in 45% and 57% of the subjects [5]. The estimate is unlikely to overpredict the incidence since 50% of the exercising, immersed divers experienced POT after a six-hour exposure to pO_2 = 130 kPa [32]. Such a dive would give 560 UPTD and K = 142. On the other hand, four hours of pO_2 = 140 kPa seems to be acceptable for at least five consecutive days of exposure [31,33]. This would parallel 384 UPTD or K = 70. The expected incidence of POT would be 16% after such an exposure [5]. A few studies have reported changes in spirometric indices on patients receiving hyperbaric oxygen (HBO_2) treatment. While hyperoxic exposure monitoring in HBO_2 treatment is beyond the scope of this work, the studies add some knowledge to the pulmonary effects of repeated hyperoxic exposures. Thorsen et al. [37] measured the pulmonary function in 20 patients receiving one daily HBO_2 treatment for 21 consecutive days. Oxygen was breathed for 90 minutes at 240 kPa. A five-minute air break was taken after every 30 minutes of O_2 breathing. This exposure corresponds to 270 UPTD or K = 111. FEV_1 and mid-expiratory flow rates remained statistically decreased for four weeks after finished treatment (last time of measurement). Though DLCO temporarily decreased during treatment, it was normalized four weeks after finished treatment. Hadanny et al. [38] reported findings from a similar study with less hyperoxia. This study included 88 patients each receiving 60 HBO-treatments of 90 minutes at 203 kPa (2 atm). Five-minute air breaks were given after every 20 minutes of oxygen breathing, with treatment given for five days a week. This corresponds to 225 UPTD or K=50 per session. In this study there was a minimal though statistically significant increase in FVC and peak expiratory flow (PEF) at the end of the treatment period.

Finally, Pott et al. [39] found no changes in 14 patients receiving one daily HBO_2 treatment for 25 consecutive days with pO_2 = 243 kPa (2.4 atm) for 90 minutes without air breaks (273 UPTD, K=123). These HBO_2 studies should be interpreted with caution in relation to manned diving. With the exception of the Pott et al. study [39], the other two [37,38] included air breaks. Adding air breaks during hyperoxic breathing significantly attenuates the POT [27,28]. Equally important, the HBO_2 studies included resting patients rather than exercising subjects. As mentioned earlier, exercise increase POT compared to resting conditions [32]. With these caveats the HBO_2 studies still indicate that approximately 270 UPTD and K = 120 can be tolerated for weeks. The data thus support the 300 UPTD daily limit recommended by many training organizations for recreational divers.

Arieli et al. recommended hyperoxic exposure to be limited to K = 244. Based on the findings of Shykoff [32] we believe that this threshold is too high – at least based on the symptoms and findings in breathing oxygen continuously at 130 to 140 kPa. We suggest that the hyperoxic exposure should be limited to K = 120 per day if no more than two consecutive days of diving takes place and there is a minimum of two days off hyperoxic exposure. For multiday exposure the daily dose should be limited to K = 70, and two days should be allowed for recovery after five consecutive days of diving. There is insufficient data to substantiate a guidance for multiday diving when no recovery days are planned for, but K = 40 to 50 is suggested in the absence of other data. This would compare to a UPTD restriction of 291 to 326 for a continuous exposure to 140 kPa and would thus be in the same order as previously suggested in the Repex guidance [24]. Diving with pO_2 lower than 50 kPa is not expected to affect recovery and could take place irrespective of these restrictions. These recommendations are intended for surface-oriented diving only – not HBO_2 treatment or saturation diving.

CONCLUSIONS

We have not been able to identify an index of hyperoxia that would allow reliable prediction of POT in all ranges of time and pO_2 relevant for surface-oriented diving. No single index reliably predicts development of VC during exposure and recovery based on time and pO_2. We would advise that the Arieli K index should replace UPTD for tracking of hyperoxic exposure in surface-oriented diving. The results (Table 5) show that Arieli K has a better performance compared to UPTD in predicting VC development during hyperoxic exposure for most relevant ranges of pO_2 and exposure time. Furthermore, Arieli K performed well regarding recovery after hyperoxia in contrast to the UPTD, which does not take recovery into account.

Recommendations for complex hyperbaric hyperoxic profiles have been based on findings from exposures to constant-level hyperoxia because data for complex profiles are not available. We suggest a limitation of K = 120 for two consecutive days of hyperoxic exposure if followed by at least two days of recovery. Exposure should not exceed K = 70 per day for a maximum of five consecutive days of diving, and two days should be allowed for recovery after this. If multiday dives without breaks are planned, the daily exposure should be limited to K=40-50.

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