Oxygen, the lung and the diver: friends and foes?

Pieter-Jan A.M. van Ooij[1,2], Peter J. Sterk[2] and Robert A. van Hulst[3]

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Affiliations: [1]Diving Medical Center, Royal Netherlands Navy Den Helder, The Netherlands. [2]Dept of Respiratory Medicine, Academic Medical Centre, University of Amsterdam. [3]Laboratory of Experimental Intensive Care and Anesthesiology, Academic Medical Centre, University of Amsterdam.

Correspondence: P.J.A.M. van Ooij, Diving Medical Centre, Royal Netherlands Navy, PO Box 10.000, 1780 CA Den Helder, The Netherlands. E-mail: Pjam.v.ooij.01@mindef.nl

ABSTRACT   Worldwide, the number of professional and sports divers is increasing. Most of them breathe diving gases with a raised partial pressure of oxygen (P_{O_2}). However, if the P_{O_2} is between 50 and 300 kPa (375–2250 mmHg) (hyperoxia), pathological pulmonary changes can develop, known as pulmonary oxygen toxicity (POT). Although in its acute phase, POT is reversible, it can ultimately lead to non-reversible pathological changes. Therefore, it is important to monitor these divers to prevent them from sustaining irreversible lesions.

This review summarises the pulmonary pathophysiological effects when breathing oxygen with a P_{O_2} of 50–300 kPa (375–2250 mmHg). We describe the role and the limitations of lung function testing in monitoring the onset and development of POT, and discuss new techniques in respiratory medicine as potential markers in the early development of POT in divers.

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To prevent the early development of pulmonary oxygen toxicity divers must be properly monitored
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Introduction

"When I breathe deeply I got a burning sensation behind my sternum and it hurt; this doesn't feel good!"

These words are from a patient we treated with hyperbaric oxygen for his severe decompression illness. Similar to this patient, thousands of patients worldwide are breathing 100% oxygen under normobaric or hyperbaric circumstances (here referred to as "hyperoxia") as part of their (adjuvant) treatment. For example, oxygen is used during the initial treatment in trauma care [1] and supportive usage of oxygen is advised in the end stage of chronic obstructive pulmonary disease (COPD) to reduce mortality [2]. In addition, as indicated by the Undersea and Hyperbaric Medical Society (North Palm Beach, FL, USA), administration of oxygen under hyperbaric conditions (hyperbaric oxygen therapy) is increasingly used as adjuvant therapy for (among other conditions) chronic diabetic ulcers, comprised grafts and flaps, delayed radiation injuries and necrotising soft tissue infections [3]. However, on a daily basis, professional and military divers also subject themselves to hyperoxia due to their occupational activities. Although the risk of developing pulmonary oxygen toxicity (POT) as a sports diver is low, there is a specific group of sports divers, the so-called technical sports divers,

who voluntarily use breathing gases with a higher partial pressure of oxygen (P_{O_2}) (oxygen, nitrox (nitrogen–oxygen) or heliox (helium–oxygen)); these divers are often unaware of the hazards that they are exposed to. Therefore, on a regular basis, these patients and divers are subjected to the risk of POT.

Another important effect of hyperoxia that endangers diving is cerebral or central nervous system (CNS) oxygen toxicity. As some divers also dive with nitrox and heliox they run a risk of CNS oxygen toxicity. While submersed and using breathing gasses with a P_{O_2} of $\geqslant$ 140–170 kPa (1050–1275 mmHg) CNS oxygen toxicity can develop, with related symptoms such as vomiting, dizziness and, ultimately grand mal seizures. Especially the latter condition can be life-threatening should it develop under water. However, as this important topic is beyond the scope of this review on POT, we refer the reader to other studies on CNS oxygen toxicity [4, 5].

In this concise review, we discuss the effects of hyperoxia on the lung of divers, how we can prevent its pulmonary toxic effects, and present some possibilities for the future.

Pathological effect of oxygen

"Oxygen, which at the tension of the atmosphere stimulates the lung cells to activate absorption, at a higher tension acts as an irritant, or pathological stimulant, and produces inflammation." [6]

With this statement, James Lorrain Smith ended his extensive paper on the toxic effects of oxygen on the respiratory system [6]. When animals were exposed for 4 days to a P_{O_2} of 74 kPa (555 mmHg), pulmonary pathological changes (*e.g.* extreme congestion of the lung, alveolar exudation and inflammation) were found. However, exposure to oxygen with a P_{O_2} as low as 42 kPa (315 mmHg) did not lead to pulmonary problems. Furthermore, the development of POT was delayed when animals were subjected to intermittent exposure to hyperoxia [6].

These results have been confirmed by many other researchers [7–9]. Over time it became clear that the pathological pathway of POT in animals had a biphasic development, *i.e.* an acute phase, followed by a chronic phase if oxygen breathing was continued [10–13]. During the acute phase, exudation appears to be a key feature, which expresses itself as interstitial and alveolar oedema. Due to this feature the acute phase is often referred to as the exudative phase. Beside exudation, pathological changes like loss of alveolar epithelial type 1 cells, destruction of pulmonary capillary endothelium, lymphatic distention, alveolar septal oedema, and acute inflammatory cell infiltrates can be found [14, 15]. Depending on the species of animal and the P_{O_2} level, the acute exudative phase can start after 8 h of oxygen breathing [16, 17] and persists for 5–12 days if oxygen exposure is continued [11, 15]. Although these lesions can be life-threatening, if oxygen breathing is discontinued these pathological changes are reversible [14]. If the animal keeps on breathing oxygen the exudative phase transforms itself to the proliferative phase. This phase is marked by the increment of alveolar type 2 cells, which replaces almost all of the damaged type 1 alveolar cells [18]. As a result, the blood-air barrier thickens up to 4–5 times [19, 20]. Furthermore, fibroblast infiltration, intra-alveolar hyaline membranes, invasion by macrophages, increase in collagen content, intra-alveolar septal scarring, and decrease in alveolar air volume is observed [14, 15]. In contrast to the exudative phase, the proliferative phase is not reversible when exposure to hyperoxia is stopped [15].

Susceptibility to POT varies widely among species but is also dependent on age, strain and individual susceptibility [10, 11, 21]. Human lungs exposed to high concentrations of hyperoxia show a sequence of pathological changes similar to those seen in primates [15]. However, compared with monkeys, (quantitatively) capillary damage and interstitial fibrosis seem to be more prominent in man, suggesting a relatively greater susceptibility of humans to POT [22].

In humans, the exudative phase starts with tracheobroncholitis, which can develop within 24 h of oxygen breathing [21, 23, 24]. The rate at which POT develops is directly related to the inspired P_{O_2} [10, 21]. Tracheobroncholitis develops after a latent period of 4–22 h when breathing oxygen with a P_{O_2} of 95 kPa (713 mmHg), but may occur as early as 3 h while breathing oxygen at 300 kPa (2250 mmHg) [21, 24]. After 24 h, the capillary endothelium and alveolar type 1 cells disrupt, as a result of which the pulmonary interstitium becomes oedematous and fibrin membranes may form along the alveolar lining [25]. Depending on the P_{O_2}, the exudative phase can be found up to 5.5 days of continued oxygen breathing. After the exudative reaction subsides, the proliferative phase marks its starts with the proliferation of interstitial fibres and alveolar type 2 cells [25]. In the late proliferative phase interlobular septal oedema, alveolar hyperplasia and fibroblastic proliferation with early fibrosis can be found [10, 11]. Oedema and fibrosis are late and end-stage processes in human POT [23]. Patients who survived were found to have developed interstitial fibrosis, emphysema, patchy areas of atelectasis and cystic bronchiolectasis [14]. Table 1 presents a more comprehensive list of pathological changes found in primates and in humans.

TABLE 1 Time of onset of pathological findings of pulmonary oxygen toxicity (POT) in primates and humans

Day	POT phase	Primates	Day	POT phase	Humans
1			1		Tracheobroncholitis, mucous flow decreased
2	Exudation	Alveolar oedema, septal wall oedema, distention lymphatic vessels, decrement alveolar type 1 cells	2–5	Exudation	Denuded alveolar type 1 cells, oedematous endothelial capillary cell swelling, necrosis respiratory epithelium, squamous metaplasia tracheal and bronchial mucosa, deposition eosinophilic slough, alveolar and interstitial oedema, formation hyaline membrane, cilial loss, decreased mucociliary transport
4		Resolution, formation hyaline membrane, influx inflammatory cells			
5	Proliferation	Increment alveolar type 2 cells, fibroblast infiltration	5–88	Proliferation	Proliferation of alveolar type 2 replacing alveolar type 1 cells, derangement of collagen and elastin, incorporation of hyaline membranes into the septal walls, fibroblastic proliferation, collagen fibre deposition, fibro-proliferative organisation of intra-alveolar exudate, infiltration with inflammatory cells, interstitial lung fibrosis, emphysematous alveoli with areas of fibrosis, cilial loss
8		Intra-alveolar hyaline membranes, thickening of the alveolar-capillary membrane, leukocytic infiltration, marked cellular proliferation of abnormal alveolar type 2 cells, haemorrhagic areas, accumulation of intracellular water			
12		Extravascular lung water within the pulmonary parenchyma and interstitial space, invasion of fibroblasts and macrophages			
56		Air-blood barrier thickened, increase in collagen content, intra-alveolar septal scarring, alveolar air volume diminished			

Looking at these pathological changes in humans, a resemblance can be seen to those in adult respiratory distress syndrome (ARDS) or ventilator induced lung injury (VILI). However, we must keep in mind that divers are, generally speaking, healthy individuals when exposed to hyperoxia, whereas patients receiving normobaric oxygen at levels that might introduce pulmonary pathological changes, are severely ill. The latter condition introduces some potential problems. Mechanical ventilation itself introduces changes that might mimic the effect of hyperoxia [26, 27]. Moreover, it is unknown whether normobaric hyperoxia in septic patients has a protective or a deteriorating effect on immunity and, thus, on the development of POT [28, 29]. Therefore, regarding the development of POT, we cannot extrapolate the results from intensive care unit patients (with ARDS or VILI) to that those in healthy persons, or vice versa.

Effect of diving on the respiratory system

"One possible way for immersion to influence lung compliance would be via intrathoracic blood pooling. Such blood pooling is likely to cause an engorgement of the pulmonary capillaries, and it is feasible that such an engorgement might have an erectile effect and lead to stiffening of the lungs." [30]

All findings already mentioned related to the pathological changes in humans came from studies performed under dry normobaric or hyperbaric circumstances. However, because divers perform their activity under water, the effect of submersion could play an additional or even reinforcing role in the development of POT. Therefore, the effect of submersion needs to be discussed.

First of all, when the human body is submersed (i.e. in toto under water) or immersed (partially under water, mostly up to the thorax or neck) hydrostatic pressure will have some effect on the body. In the presence of hydrostatic pressure, there is a redistribution of 500–800 mL of blood from the legs to the large veins and pulmonary vessels [31]. Due to intra-thoracic blood pooling, the ventricular wall stretches and the length of the cardiac muscle increases. This latter mechanism augments the cardiac muscle contractile force, which raises the cardiac output (the so-called "Frank Starling mechanism") [32]. Thereafter, an increase in pulmonary blood flow, pulmonary arterial pressure and pulmonary vascular volume takes place, as described by DAHLBÄCK et al. [30]. Moreover, when a person is immersed in cold water, vasomotor activity shifts extra peripheral blood to central parts of the body, which increases the blood volume shift [33]. As a result of the above-mentioned phenomena, the lung will become stiffer [30]. In addition, an increase in pulmonary artery pressure and in central blood volume also increases apical perfusion, resulting in augmented lung perfusion and an increased pulmonary exchange area [34, 35]. Secondary, the intra-thoracic blood pooling itself will influence the neuroendocrine diuretic system, which will lead to immersion-induced diuresis and a decrease in plasma volume of approximately 13% [32, 36–38].

Secondly, apart from submersion, the combination of the posture of the diver and the characteristics of the breathing apparatus can lead to hydrostatic imbalance. This is the pressure difference of the breathing apparatus mouth pressure and the lung centroid pressure [39]. When a diver is in a prone position and using a rebreather, in oxygen diving, the "counter lung" of his diving apparatus is situated under the diver. Swimming in such a position would lead to a higher pressure in this counter lung compared with the lung centroid due to the hydrostatic pressure. This relatively higher pressure will lead to a small decrease of the opening pressure and ultimately to a slightly positive static lung load. However, when the diver is in an upright position, he or she will not benefit from the position of the counter lung and has to overcome the normal opening pressure which is somewhat higher than in the prone position. All together there will be more imbalance in the upright dive situation compared with the prone situation [31].

Although the effect of submersion on pulmonary physiology seems to be a theoretical problem, our earlier study demonstrated that diffusing capacity was more impaired after a submersed oxygen dive than after a comparable non-submersed (chamber) dive [38]. This suggests that POT develops to a greater extent in a submersed hyperbaric environment.

Taking this into account, it is of paramount importance to perform studies under the same condition as the diver is operating in, *i.e.* submersed. Only then can one truly elucidate the development of POT in divers.

Preventing pulmonary oxygen toxicity in divers

> "*On the basis of all existing information, change in [vital capacity] was selected as the index which best reflected the onset, rate of development and degree of severity of pulmonary effects produced by oxygen toxicity in man.*" [40]

As POT is a toxic progress that could become rapidly progressive one has to monitor divers who might be subjected to it. As the lung is the first organ that encounters the toxic effects of inhaled oxygen [11, 24], it is logical to look for changes in any lung-related complaints or lung function parameters as a marker for the onset and development of POT. It is often suggested that symptoms of POT (cough, chest pain when breathing and dyspnoea) precede changes in pulmonary function tests and are likely to be a more sensitive indicator of the effect of POT than changes in pulmonary function [21, 41]. However, the rate of development of these symptoms is so variable that it is considered a poor index of O_2 tolerance [21]. For this reason, lung functions parameters are considered a more objective monitoring index.

Many lung function parameters have been studied regarding their usefulness for identifying POT. Of all lung function parameters, none of them has been studied so often as the vital capacity (VC). As early as 1939 BECKER-FREYSENG and CLAMMAN [42] noted a decrease in VC after 24 h of 90% oxygen breathing at normobaric pressure whereas breathing oxygen below 60% did not generate any toxic effect. This decrease in VC was confirmed by others [10, 11, 16, 23, 43, 44]. However, it was the series of studies by CLARK and LAMBERTSEN and colleagues that finally showed its usability in monitoring POT. Between the 1970s and 1980s, they performed several studies on divers who were subjected to increasing levels of oxygen of up to 300 kPa (2250 mmHg) [40, 44–46]. In all of these studies, they observed a decrease in VC. By integration of the decrement in VC with P_{O_2} and dive time it was possible to develop pulmonary tolerance curves [40]. Using these curves, it was possible to predict the median decrease in VC given the dive time and P_{O_2} of the breathing gas the diver used. Although these curves were meant to be used for daily professional diving, it provided only a rough estimation of the degree of POT a diver developed and lacked the accuracy required.

In 1971 BARDIN and LAMBERTSEN [47] designed the concept of a quantitative unit of pulmonary toxic dose (UPTD) [48]. Based on the pulmonary tolerance curves they designed a mathematical model. In this model one UPTD is the degree of pulmonary poisoning produced by breathing 100% oxygen continuously at 101 kPa (758 mmHg) for 1 min. As demonstrated previously, the upper non-toxic limit was set at a P_{O_2} level of 50 kPa (375 mmHg). Any oxygen breathing below this level was considered to have no measurable effect on VC [49, 50]. The total amount of UPTD for continuous oxygen exposure at a single pressure could be calculated using the following equation [48]:

$$UPTD = t \cdot \sqrt[-1.2]{\frac{0.5}{PO_2 - 0.5}}$$

Once the amount of UPTD is calculated, this number must be compared with a reference table (table 2), which relates the dose to the predicted percentage of decrease in VC [48, 51]. The maximum UPTD for ordinary professional diving is 615, whereas the upper limit for a single exceptional exposure is set at 1425 UPTD [48]. Nowadays, in the diving society, this UPTD model is generally accepted and every professional diver asks about the UPTD when discussing oxygen and diving. Indeed, a decrease in VC is considered the "gold standard" with regard to the monitoring of POT development.

UPTD	% median decrease in VC
615	2
825	4
1035	6
1230	8
1425	10
1815	15
2190	20

TABLE 2 Corresponding median decrease in vital capacity (VC) based on total units of pulmonary dose (UPTD)

Data from [48].

Shortly after the introduction of the UPTD model it received some criticism. For example, it failed to take any recovery into account and, when performing multiple dives per day, it was not possible to calculate the UPTD [50, 51]. Updated and new models were introduced in which recovery and multiple dives were combined [51–53]. Noteworthy is the study by ARIELI *et al.* [53]: using data from published studies [45, 46, 54] they developed a model which not only calculated the expected decrease in VC but also incorporated a formula to calculate the recovery time from this decrement. At the moment, this remains the most sophisticated VC-based model.

VC or not VC: that is the question

"[Diffusion capacity of the lung for carbon monoxide] *therefore seems to be a more sensitive indicator of oxygen toxicity than the classic vital capacity.*" [55]

The median decrease in VC and its derived UPTD concept are widely used in professional and military diving as preventive guidelines [56]. In their thesis, CLARK and LAMBERTSEN [40] extensively described which parameters could best be used. Besides VC, they considered the use of inspiratory capacity, inspiratory flow rates, diffusion capacity of the lung for carbon monoxide (D_{LCO}), pulmonary blood volume and lung compliance. Because pulmonary oxygen toxicity can develop very quickly, they decided that accuracy, speed and convenience of the measurement should be the prerequisites for an effective marker. However, based on these prerequisites, only the use of VC met their criteria. Inspiratory capacity was disregarded because it was more time-consuming compared to measurement of VC, and inspiratory flow rates appeared to be less sensitive than VC. The measurement of D_{LCO} and pulmonary blood flow was time consuming, and their sensitivity was considered to be less when compared to VC. In addition, to properly measure D_{LCO} and pulmonary blood flow, appropriately trained personnel are required. Finally, lung compliance was also disregarded, as it did not meet the criteria of convenience. An important advantage of the measurement of VC was that it is easily learned by laymen and, with the use of portable apparatus, it can also be used on site.

Since the first introduction of the VC concept, and its derived UPTD concept it was emphasised that both concepts have their limitations. HARABIN *et al.* [51] concluded that, due to the intra- and inter-individual variations in VC, small changes in this measure cannot be captured. Repetitive measurements of VC show a coefficient of variation of 2.5%–5.7% even in healthy subjects [51, 57]. Thus, only an exposure to oxygen comparable to an UPTD load of 1035 units or more would lead to clinically relevant changes. As most of the occupational dives are well under an UPTD load of 1035 units, it is important to have a monitor index that can capture clinically relevant changes at this kind of operational level. Furthermore, all data used for modelling the VC concept were derived from dry hyperbaric exposures. This raises the question whether the "gold-standard" is appropriate for submerged oxygen diving. As expected, it appeared that the decrement in VC is a poor predictor for in-water oxygen dives or short oxygen exposures [38, 41]. Therefore, even sophisticated models (like that of ARIELI *et al.* [53]) still face these limitations when used for submerged oxygen diving.

In the last decades, the "classical" measurement techniques used in lung function testing (*e.g.* spirometry and diffusing capacity) have undergone major improvements. Therefore, it is a good moment to examine whether the aforementioned lung function parameters by CLARK and LAMBERTSEN [40] can meet the required criteria of accuracy, speed and convenience. POT can lead to many pathological pulmonary alterations which, in turn, can lead to specific changes in lung function parameters (table 3). However, of all the lung function parameters, only diffusing capacity was considered to be a viable alternative option [55, 56, 59]. As discussed before, the area of damage related to POT is the alveocapillary membrane. Since changes in

TABLE 3 Pathological findings in pulmonary oxygen toxicity and their changes in lung function parameters

Pathological changes	Increase in parameter	Decrease in parameter
Interstitial oedema		VC, D_{LCO}, $C_{L,st}$
Alveolar oedema		VC, D_{LCO}, $C_{L,st}$
Pulmonary capillary fibrin thrombin		VC, D_{LCO}, F_{eNO}
Loss of alveolar type 1 cell		VC, D_{LCO}, $C_{L,st}$
Neutrophilic infiltration	F_{eNO}	F_{eNO}
Capillary endothelial lesions		VC, D_{LCO}, $C_{L,st}$
Interstitial distention		D_{LCO}
Increase alveolar type 2 cells	$C_{L,st}$	D_{LCO}
Infiltration inflammatory cells	F_{eNO}	
Haemorrhage		D_{LCO}

VC: vital capacity; D_{LCO}: diffusing capacity of the lung for carbon monoxide; $C_{L,st}$: static lung compliance; F_{eNO}: exhaled nitric oxide fraction. Data from [58].

diffusing capacity represent any deviation at this anatomical level, it is obvious why diffusing capacity is preferred. This is supported by recent studies performed by our group; our data suggest that using VC is not sufficient in the assessment and monitoring of POT in oxygen divers and that changes in diffusing capacity for either carbon monoxide or nitrogen monoxide (D_{LNO}) may be more informative [38, 60].

The question then arises as to whether the diffusing capacity model can replace the VC model in monitoring POT; apparently, not yet. Firstly, it lacks sufficient data to develop a dose-response model like the one in VC. Secondly, the method to measure diffusing capacity introduces bias. Factors such as the stability of the gas analyser, inhalation mode, whether or not Valsalva or Muller manoeuvres were performed during the breath-hold phase, or the simple reason that diffusing capacity is determined using two different oxygen concentrations, could be of influence [61]. Furthermore, although the affinity of carbon monoxide for haemoglobin (Hb) is more than 200-times greater than for oxygen, an overload of oxygen diminishes this affinity of carbon monoxide leading to a decrease in CO-Hb [62–64]. Because supplemental oxygen breathing affects the measurement of D_{LCO}, it is recommended to wait at least 10 min before performing a D_{LCO} test after using (supplemental) oxygen [61]. Finally, as stated by CLARK and LAMBERTSEN [40], an index for professional use must be accurate, convenient and fast enough to perform any measurement. Although the measurements can be produced at an accurate level using the American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines [61], and modern diffusing capacity devices are much faster than 20–30 years ago, they still miss some convenience regarding the apparatus itself. For example, unlike the spirometry apparatus, the devices for diffusion of carbon monoxide were (until recently) not portable. Therefore, all measurements had to be performed in a laboratory setting; moreover, because the laboratory was (generally) not close to the diving research location, delays were introduced between the end of exposure to oxygen and the moment of measurement. However, some of these problems can be solved by using D_{LNO} instead of D_{LCO}. The main advantage of the D_{LNO} method compared with the D_{LCO} method is the absence of an interaction between nitrogen monoxide and oxygen [65]. This allows researchers to measure acute changes on the alveolocapillary membrane after oxygen exposure. In addition, inhaled nitrogen monoxide levels up to 67 ppm do not affect any D_{LNO} measurement [66], although high levels of inhaled nitrogen monoxide lead to vasodilatation of the pulmonary capillary vessels and can confound results [67]. Finally, as with the apparatus to measure D_{LCO}, no portable D_{LNO} apparatus is currently available.

Because the VC model cannot adequately assess and monitor POT, and the diffusing capacity models are still in the developmental stage, is there anything else we can use to minimise the risk of the toxic effects of hyperoxia? If the answer to this question is "no", this represents a problem for thousands of divers using oxygen-enriched mixtures or oxygen as a breathing gas. Fortunately, with regard to POT, it is not man that is the limiting factor, but the apparatus itself. Firstly, the absorbent for carbon dioxide (soda lime) that the rebreather uses has a limited duration. Although soda lime can be used for 4–6 h, under operational circumstances this is generally limited to about 2–3 h. Secondly, military oxygen divers increasingly use diver propulsion devices. These devices have a battery-powered electric motor which drives a propeller and, generally, the batteries last about 2–3 h. Based on a normal oxygen diving depth of 3–5 m of seawater (msw), a dive time of 2–3 h will be within the POT limits [68].

Bearing in mind the limitations of these devices, the UPTD model can still be used. However, since technical developments are rapid in this field, these device-related restrictions will probably soon be solved. When this eventually happens it will not be the equipment, but humans, that will be the limited factor.

At that time, we will need to have an effective model that allows prevention of POT in our divers who are breathing oxygen.

Future perspectives in monitoring POT

"*The results show that an oxygen dive to 9 msw for 1 h produces a distinctive VOC breath print, which mainly consists of methyl alkanes*". [69]

In the field of respiratory medicine, increasing use is made of molecular exhaled breath analysis. Nowadays, the fraction of exhaled nitrogen monoxide (F_{eNO}) can be used in the treatment of asthma; it is easy to use, measures exhaled nitrogen monoxide very quickly and is very convenient. As F_{eNO} is associated with inflammation of the lower airways, it is feasible that inflammation due to POT will also lead to changes in exhaled nitrogen monoxide. Studies using F_{eNO} after hyperbaric oxygen exposure reported inconsistent results [70–74]. One of these studies measured F_{eNO} after hyperbaric oxygen exposure during immersion [74]; although a significant decrease in F_{eNO} was found it fell within the limits of biological variation.

The main limitation of F_{eNO} as an index for POT is the standardised exhaled flow rates. According to the ATS guidelines [75] a flow rate of 50 mL·s^{-1} should be used. This flow rate is of special interest in monitoring asthma as it preferentially measures changes in nitrogen monoxide derived from the conductive compartment (trachea ⩽17th airway generation), which play an important role in monitoring the treatment of asthma [76]. However, because pulmonary oxygen toxicity is situated in the alveolocapillary compartment, a flow rate of 50 mL·s^{-1} is unlikely to provide adequate information about ongoing process in this compartment. Flow rates of at least 250 mL·s^{-1} should be used to acquire information about this specific compartment [77, 78]. This implies that, if the effect of POT on the alveolocapillary membrane is the subject of study, the multiple exhalation flow technique should be used [79]. However, until now, no studies have been performed in which the multiple exhalation flow technique was used after immersion during hyperoxic exposure.

Another promising technique is the measurement of volatile organic compounds (VOC). Measuring changes in VOC allows to make VOC breath prints, which can be disease-specific [80, 81]. Breath prints have been identified that can be used for the assessment of diseases like lung cancer [82–84], infectious diseases like tuberculosis [85], and inflammatory conditions such as asthma [86, 87] and COPD [87, 88]. Changes in VOC were also found after hyperoxic exposure [69, 84, 89, 90]. The changes in VOC most frequently observed after normobaric hyperoxia were an increase in pentane and methyl alkanes [84, 89, 90], while the VOC breath print found after submersed hyperoxia consists mainly of methyl alkanes [69]. In the latter study, because changes in VOC were found 4 h post-exposure, the pathophysiological background could be either a primarily lipid peroxidation-induced pathway or a delayed inflammatory one.

Although changes in F_{eNO} and VOC seem promising, more studies are required to determine their usefulness in monitoring POT in submerged oxygen exposure. It is important that these studies only use alveolar exhaled breath samples, which must be sampled at multiple post-exposure time intervals. Furthermore, different P_{O_2} and dive times should be included and investigated.

Conclusion

In submerged oxygen diving, it is no longer wise to use the gold standard (a decrease in VC) as a single measurement for the early development of POT, as it may underestimate the risk of developing POT for both professional and oxygen divers. This also applies to the use of UPTD or any other VC-derived model. However, because no model is available that can replace the gold standard, it is the best tool that we have at the moment. Nevertheless, its limitations should be kept in mind when using it.

Future research should focus on developing other methods to monitor the early development of POT. Also, alternative UPTD indexes based on D_{LCO} and D_{LNO} should be developed for submerged oxygen exposures. The use of VOC and F_{eNO} as markers for POT is still in its infancy. Nevertheless, as the sampling of exhaled air is very convenient, quick and simple to perform at the point of care, this might prove to be the most important method for the future.

The ultimate goal is to develop a simple and portable device based on changes in exhaled VOC and/or nitrogen monoxide. Then, by simply exhaling into this device, oxygen divers can monitor themselves to establish whether it is possible to continue oxygen diving, or whether they have to temporarily stop. To achieve this goal, effective collaboration is required between research centres such as universities, military diving medical departments and diving training centres.

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