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Review

Assessment of pulmonary oxygen toxicity: Relevance to professional diving; a review

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ABSTRACT

When breathing oxygen with partial oxygen pressures (P_{O_2}) of between 50 and 300 kPa pathological pulmonary changes develop after 3–24 h depending on the P_{O_2}. This kind of injury (known as pulmonary oxygen toxicity) is not only observed in ventilated patients but is also considered an occupational hazard in oxygen divers or mixed gas divers. To prevent these latter groups from sustaining irreversible lesions adequate prevention is required.

This review summarizes the pathophysiological effects on the respiratory tract when breathing oxygen with P_{O_2} of 50–300 kPa (hyperoxia). We discuss to what extent the most commonly used lung function parameters change after exposure to hyperoxia and its role in monitoring the onset and development of pulmonary oxygen toxicity in daily practice. Finally, new techniques in respiratory medicine are discussed with regard to their usefulness in monitoring pulmonary oxygen toxicity in divers.

1. Introduction

1.1. A bit of history

Pulmonary oxygen toxicity is a medical complication, which can occur during oxygen therapy and in professional conditions such as diving. In 1775 Joseph Priestley reported the injurious character of dephlogisticated air, or oxygen as it is nowadays called: *"Though pure dephlogisticated air might be very useful as a medicine, it might not be proper for us in the usual healthy state to the body"* (Bean, 1945; Winter and Smith, 1972; Wolfe and DeVries, 1975).

However, it took over 100 years before this statement was confirmed beyond doubt. In 1878 Paul Bert described the neurological effects of oxygen toxicity after exposing larks to 100% oxygen at 500 kPa (5 atmosphere absolute) of ambient pressure (Bean, 1945; Winter and Smith, 1972). In 1899 James Lorrain-Smith described the effect of oxygen on the pulmonary system after exposing animals to 100% oxygen at pressures up to 300 kPa (Smith, 1899). Post-mortem examinations performed on these animals exposed to oxygen revealed that the lungs were extremely congested (Smith, 1899). These pathological changes were confirmed in other animal studies conducted in the following decades (Barach et al., 1944; Bean, 1945; Clark and Lambertsen, 1971a).

In the mid-1900s, pulmonary oxygen toxicity became a serious clinical problem in ventilated patients. Due to the development of efficient mechanical ventilators these patients were ventilated with much higher concentrations of oxygen than previously used (Brewis, 1969; Fisher et al., 1984; Miller and Winter, 1981; Wolfe and DeVries, 1975). Breathing high concentrations of oxygen led to an increasing number of cases of pulmonary oxygen toxicity, some of which resulted in the death of the patient (Brewis, 1969; Miller and Winter, 1981). However, besides patients, it appeared that healthy subjects were also at risk to develop pulmonary oxygen toxicity.

1.2. Diving and pulmonary oxygen toxicity

Particularly in diving medicine pulmonary oxygen toxicity became of daily importance with the introduction of oxygen and mixed gas rebreathing diving systems. With the use of these devices divers were able to breath oxygen for several hours with partial oxygen pressures (P_{O_2}) of ≥100 kPa (Butler, 2004). A drawback of using these devices was the increasing risk of pulmonary oxygen toxicity. Therefore, understanding and dealing with the pathophysiology of diving-related problems was of increasing importance. The first extensive review focussing on the onset and development of pulmonary oxygen toxicity in divers was published by Bean in 1945 (Bean, 1945). Until the late 1930s, most of the knowledge on

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the effects of oxygen in divers was based on deep air dives in which P_{O_2} was increased to levels far above 50 kPa. However, because decompression stress (i.e. the presence of venous gas microemboli (Thorsen, 2006)) played an important role in these air dives it was unclear whether the respiratory effects were oxygen based, or simply due to decompression (Bean, 1945).

A step forward was made by Clark and Lambertsen in the 1960s and 1970s when they exposed divers to 100% oxygen with P_{O_2} levels of up to 300 kPa in a dry hyperbaric chamber (Clark and Lambertsen, 1970, 1971b; Fisher et al., 1968). Much of current knowledge on the onset and development of pulmonary oxygen toxicity in divers was derived from these latter landmark studies (Clark and Lambertsen, 1970).

1.3. Clinical symptoms of pulmonary oxygen toxicity

As reported by Lorrain-Smith, animals exposed to oxygen levels up to about 300 kPa for ≥6 h eventually died of pathological changes due to oxygen exposure. From the start until the moment the animal died, several 'clinical' symptoms related to pulmonary oxygen toxicity were observed. First, the animals became restless, which was followed by lethargy, anorexia and vomiting. When oxygen exposure was continued the animals had a laborious respiration. The terminal phase was characterized by cyanosis, and increased laboured or gasping respiration with frothy or bloody sputum, after which the animal died (Clark and Lambertsen, 1971a; Smith, 1899). However, it is impossible to extrapolate these findings to the human clinical situation because it is unknown, for example, how 6 h in the lifespan of a rat relates to that in humans.

In humans, the symptoms of pulmonary oxygen toxicity that occur during the early stages are similar to those observed in animals. When humans were exposed to 100% oxygen at 101 kPa for 24 h the first symptom of pulmonary oxygen toxicity were described as a mild substernal tickling or tracheal irritation (Clark and Lambertsen, 1971a; Comroe, 1945). This sensation was accentuated by deep inspirations and often provoked coughing (Clark and Lambertsen, 1971a). When oxygen exposure was continued for another 24 h subjects complained about chest tightness followed by progressively increasing tracheal irritation that eventually led to substernal pain and uncontrollable coughing (Clark and Lambertsen, 1971a; Clark and Thom, 2003; Lowry, 2002). Dyspnoea during exercise and later at rest developed towards the end of this early stage (Clark and Thom, 2003).

Nowadays, both clinical symptoms and changes in lung function are used to monitor the onset and development of pulmonary oxygen toxicity. This review presents an overview of the pathophysiological effects on the respiratory tract when breathing oxygen with partial pressures of between 50 and 300 kPa (hyperoxia). We also discuss to what extent the most commonly used lung function indices change after exposure to hyperoxia and what role they can play as possible markers of pulmonary oxygen toxicity. Finally, new techniques in lung function analyses are presented and their usefulness for monitoring pulmonary oxygen toxicity is evaluated.

2. Pathophysiological changes due to pulmonary oxygen toxicity

2.1. Human studies on pulmonary oxygen toxicity

Only a few histopathological post-mortem studies have investigated the onset and development of pulmonary oxygen toxicity in humans (Anderson et al., 1973; Kapanci et al., 1972; Pratt, 1958). When neonates or adults were ventilated with 100% oxygen for ≥ 30 h, denuded alveolar type 1 cells, oedematous endothelial capillary cell swelling, necrosis of the respiratory epithelium, and squamous metaplasia of tracheal and bronchial mucosa was found. Furthermore, deposition of eosinophilic slough within the bronchioles, and oedema within the alveola and interstitium was reported (Anderson et al., 1973; Bellingan, 2002; Brewis, 1969; Fisher et al., 1984; Proudfoot et al., 2011; Schuster and Kollef, 1996). Consequently, the proteinaceous oedema fluid became organized within the alveoli with the formation of hyaline membranes on the denuded membrane (Bellingan, 2002; Claireaux, 1975; Fisher et al., 1984; Schuster and Kollef, 1996; Sevitt, 1974). In addition, fibrin thrombi were formed in the pulmonary capillaries leading to dilatation and cellular infiltration of neutrophils (Fisher et al., 1984; Jackson, 1985; Klein, 1990; Pratt, 1958; Schuster and Kollef, 1996). Due to the presence of exudate, this initial phase was called the exudative phase and was found up to approximately 5 days of continued 100% oxygen exposure. If ventilation with oxygen was continued the exudative transformed into a proliferative phase, which was characterised by proliferation of alveolar type 2 cells that replaced alveolar type 1 cells. Due to alveolar replacement, the alveolar lining underwent a cuboidal transformation, which led to an increased thickening of the alveolar membrane (Jackson, 1985). Furthermore, 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 and infiltration with inflammatory cells occurred (Bellingan, 2002; Claireaux, 1975; Fisher et al., 1984; Jackson, 1985; Klein, 1990; Schuster and Kollef, 1996; Senior et al., 1971; Sevitt, 1974). Eventually, interstitial lung fibrosis or emphysematous alveoli with areas of fibrosis developed as an end stage of pulmonary oxygen toxicity (Anderson et al., 1973; Miller and Winter, 1981; Pratt, 1958; Schuster and Kollef, 1996; Sevitt, 1974).

Although these observations seem to be confirmed, it should be emphasised that the pathological findings in humans were based on post-mortem studies of ventilated patients. This introduces two problems. First, the underlying disease could influence the pathological changes found (Ballentine and Jobsis, 1968). Second, mechanical ventilation itself introduces changes, known as ventilator induced lung injury, which could confound post-mortem results and mimics the effect of hyperoxia (Altemeier and Sinclair, 2007; Carvalho et al., 1998; Gattinoni et al., 2010). In addition, ventilated patients are at risk of developing ventilator-associated pneumonia (Altemeier and Sinclair, 2007). A combination of hyperoxia and bacterial lung infection leads to deteriorating effects with respect to pulmonary oxygen toxicity (Coalson et al., 1989). Furthermore, it is still subject of debate whether hyperoxia in septic subjects has a protective or a deteriorating effect on the immunity (Baleeiro et al., 2003; Hauser et al., 2009; Hou et al., 2009). Therefore, results regarding the development of pulmonary oxygen toxicity in ICU patients cannot be extrapolated to healthy subjects like professional divers. Therefore, fully understanding the development of pulmonary oxygen toxicity requires consideration of comparative animal studies.

2.2. Animal models

Following the study of Lorrain-Smith many animal studies were performed, the majority employing rodents like mice, rats and rabbits (Clark and Lambertsen, 1971a). Although these animals are suitable, they differ from humans in their anatomical structure of the lung. Furthermore, susceptibility to pulmonary oxygen toxicity is also species-, strain- and age dependent (Klein, 1990; Wolfe and DeVries, 1975) implying a possible species-specific defense mechanism regarding pulmonary oxygen toxicity. Of all animals, the baboon is considered the most appropriate animal model to study pulmonary oxygen toxicity (Robinson et al., 1974). Similar to humans, baboons also follow a two-stage pattern of pulmonary