AEROMEDICAL REVIEWS

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Recent interest in basic biomedical research has led to many experiments involving the use of high partial pressures of oxygen. Within the past few years many experimental animals, patients, and volunteers have been subjected to high oxygen environments for physiologic studies (40, 41), space cabin experiments (101), and various therapeutic regimens (24). The risks inherent in the use of high oxygen tensions have been long known and well described, but often ignored. It is a common misconception among physicians, for instance, that the use of oxygen involves no toxic hazard.

Nearly one hundred years ago Bert (20) described the apparently paradoxical effect of increased oxygen tension depressing metabolic oxidization, resulting in a general deterioration of body metabolism. The lesions thus produced are most evident in the lungs, with congestion, edema, epithelial degeneration, and finally frank pneumonia appearing after 40 to 100 hours. In addition, there is an associated vascular congestion in all the abdominal organs (83, 98). These findings have been confirmed by many investigators (11, 23, 26, 34, 80, 85, 86, 88, 97, 99).

In acute experiments symptoms of oxygen toxicity develop as a hyperbolic relationship of partial pressure to time of exposure. Man normally receives oxygen at about 160 mm. Hg, which is about 21% of the total atmospheric pressure (760 mm. Hg). As long as the partial pressure of oxygen does not exceed 350 mm. Hg, no evidence of toxicity appears. This corresponds to the amount of oxygen an individual would receive if he inhaled 100% oxygen at 20,000 feet of altitude. Both man and experimental animals have been subjected to these decreased pressures of pure oxygen for prolonged periods without apparent ill effect (3, 19, 35, 38, 71, 72, 93).
On the other hand, there are numerous reports of oxygen toxicity occurring in human beings when oxygen is given at pressures exceeding 350 mm. Hg. Comroe et al. (33) found that volunteers subjected to 760 mm. Hg (100%) oxygen for 24 hours developed irritation of the lungs, paresthesia, and conjunctival irritation. Becker-Freyseng (13) subjected himself and Clamann to 680 mm. Hg (90%) oxygen for 65 hours. Clamann developed paresthesia of the fingers in 24 hours; Becker-Freyseng experienced similar symptoms after 48 hours. The experiment was terminated after 65 hours when continuous vomiting developed in one of the investigators, who subsequently required hospitalization for pneumonia.

Reinhard et al. (92) administered 530 to 760 mm. Hg (70 to 100%) oxygen by nasal mask to patients with sickle-cell anemia for periods of 8 to 20 days. Patients complained of numbness and tingling of hands, anorexia, intense headaches, nausea and vomiting, impairment of hearing, epistaxis, and swelling and edema of mucous membranes. No eye studies were done, but no visual complaints were recorded.

In addition, new evidence of oxygen toxicity continues to appear in the literature with great regularity. Ernsting (48), in 1960, and Langdon and Reynolds (67) in 1961, noted respiratory problems in jet pilots who had inhaled oxygen while experiencing high G-forces. In 1962, Gable and Townsend (52) reported pigment and structural changes in lung tissue taken from jet pilots who had experienced prolonged exposure to pure oxygen.

After reviewing the literature, Mullinax and Beischer (74) suggested that 12 hours should be the maximum limit for breathing pure oxygen at normal pressures. Behnke et al. (16) set the limit of "comparative safety" at 4 hours. In spite of this, there must be a wide margin of safety. Boothby et al. (25) stated that they administered 760 mm. Hg of (100%) oxygen to more than 800 patients for as long as 48 hours without producing ill effects.

Increasing the partial pressure of oxygen presented to the body greatly accelerates the appearance of toxic symptoms. The symptoms produced under increased pressure are primarily of the
Central nervous system and include convulsions, euphoria, and paresthesia (16, 17, 45). Donald (43) found that oxygen at 4 atmospheres (3,000 mm. Hg) produced symptoms within 6 minutes. Thus, at 1 atmosphere the toxic symptoms primarily involve the pulmonary system, while at increased pressures symptoms of the central nervous system predominate (85).

Extreme variation in the susceptibility of different individuals to oxygen toxicity has been found to be a major factor in both human and animal experiments (13, 42, 43). This individual variability makes it difficult to evaluate conflicting reports and, in the past, has contributed substantially to confusion concerning oxygen toxicity.

The effect of oxygen on the visual mechanism is a special aspect of oxygen toxicity. The role of high oxygen environments in the pathogenesis of retrolental fibroplasia is well established. Moreover, recent studies indicate that irreversible ocular damage may occur in mature animals after prolonged exposure to high partial pressures of oxygen. The purpose of this review is to summarize the available literature on oxygen pertaining to the visual mechanism. Other aspects of oxygen toxicity have been well reviewed by Bean (12) and Stadie et al. (99).

**OCULAR PHYSIOLOGY**

**Aqueous**

The physiology of oxygen in the eye has been well studied. De Haan (55) measured the oxygen tension in the aqueous humor of rabbits by using Krogh's microtonometric technic. He found the tension to be 20 to 30 mm. Hg, but recognized that some loss of oxygen from the aqueous humor occurred during the analysis through auto-oxidation. Correcting for this loss, he concluded that the oxygen tension was probably nearer 40 or 45 mm. Hg.

Fischer (50) measured the change in oxygen within a glass chamber sealed to the anterior segment of the eye. He observed a loss of oxygen from the chamber, but in similar experiments, in
which the anterior chamber was filled with nitrogen, he could not
detect an outward movement of oxygen into the chamber. He
concluded that the corneal epithelium acts as a barrier to oxygen
but that it can utilize oxygen from the air.

Friedenwald and Pierce (51) analyzed the composition of bub-
bles introduced into the anterior chamber of a dog. They found
that the gas in the bubble quickly comes into equilibrium with the
gases in the aqueous. They determined the partial pressure of
oxygen in the aqueous to be 47 mm. Hg. When the optic nerve
was severed and allowed to atrophy, no changes in gas pressures
were noted. For this reason, they concluded that the retina carries
on its exchange of gases almost exclusively through its own blood
vessels and has no influence on the gas content of the aqueous.
They also found that covering the cornea with a contact lens had
no effect on the aqueous oxygen equilibrium. Drenckhahn and
Lorenzen (44) noted a 5% decrease in aqueous PO\textsubscript{2} under similar
conditions. Friedenwald and Pierce (51) further noted that the
oxygen tension of the posterior chamber was 80 to 90 mm. Hg
when the lens was removed. From this difference in PO\textsubscript{2} between
the anterior and posterior chamber, they calculated that the lens
consumed from 0.2 to 0.5 mm.\textsuperscript{3} of oxygen per minute.

Heald and Langham (57) carefully studied the permeability of
the cornea and blood aqueous barrier to oxygen. They experi-
mented with rabbits and used polarographic methods for oxygen
determinations. With these techniques, the diffusion rate of oxygen
across the cornea in the inward and outward directions was found
to be equal. Removal of the epithelial and endothelial layers did
not significantly change the diffusion rate.

In studying the aqueous, it was also noted that the mean
oxygen tension of anesthetized animals was 48 mm. Hg, while in
conscious animals the mean tension was 55 mm. Hg.

By exposing the cornea alone to 760 mm. Hg of oxygen, while
maintaining the animals' normal respiration with room air through
a tracheal tube, the PO\textsubscript{2} of the aqueous was increased to 131 mm.
Hg. Furthermore, by supplying oxygen through a tracheal tube,
while the animals were maintained in room air, the PO$_2$ of the aqueous was increased to between 130 and 165 mm. Hg (44; 57). Measurements of aqueous PO$_2$ with the animals enclosed in an environment of pure oxygen were not found in the literature. However, rabbits enclosed in a chamber with 720 mm. Hg oxygen and 40 mm. Hg carbon dioxide (5%) developed an aqueous PO$_2$ of 258 mm. Hg after 3 hours. Since the vasodilatory effects of this amount of carbon dioxide are powerful and conflict with the vasoconstriction caused by high oxygen tensions, it is difficult to evaluate these findings.

Cater and Silver (31) found, however, that the ratio of the tissue PO$_2$, when the animal was breathing oxygen, to the tissue PO$_2$, when the animal was breathing air, was a constant of mean value 2.1 to 2.3 for the tissues studied. A constant calculated with the PO$_2$ values found by Heald and Langham (57) for the aqueous and by Krause and Goren (66) for the vitreous would be about 2.6 to 3.4. This is considerably higher than the values found in other tissues (1), and this may help to account for the fact that the eye is often the target organ of oxygen toxicity, as shown by development of retrolental fibroplasia and reported in many experimental studies.

Vitreous

Krause and Goren (66) studied the oxygen tension of the vitreous humor of the cat by using polarographic methods. Unfortunately, they removed the cornea, drained the aqueous, and retracted the lens to insert the electrode, thereby destroying any oxygen equilibrium between the vitreous and the aqueous. Further, this must have allowed direct exposure of the vitreous and the aqueous and of the vitreous to oxygen in some of the experiments. Nevertheless, they found that the oxygen tension of the vitreous under normal atmospheric conditions equaled 53 mm. Hg. When the animal was placed in a pure oxygen environment, the PO$_2$ rose to 177 mm. Hg within 45 minutes. After the animal was removed from a high oxygen environment, the PO$_2$ quickly returned to normal.
Patz (82) recorded the oxygen tension at the retinal surface in the adult cat following occlusion of the central retinal arteries by photocoagulation. The oxygen tension quickly dropped to near zero levels. Administration of 100% oxygen resulted in a measurable increase in the partial pressure of oxygen. From these studies, he concluded that the diffusion of oxygen to the retina could be substantially increased if the subject inhaled pure oxygen. When pure oxygen was used clinically, patients with retinal arterial occlusion had an immediate, striking improvement in vision. When it was used over a longer period, however, the benefits were less pronounced and there was no improvement in the final result of the injury.

Retinal vessels

The effects of oxygen on retinal vessels have been observed. Cusick et al. (37) measured the caliber of retinal vessels after breathing oxygen at 760 mm Hg for 30 minutes. They noted a diminution in caliber of between 10.5 and 37.7% for arterioles and between 16.2 and 37% for the veins. The diminution averaged 24% for arterioles and 38.2% for veins.

Other investigators have made similar observations (35, 37), but Duke-Elder (46) was unable to detect any change in the size of retinal vessels in subjects breathing pure oxygen more than 5 minutes. Cusick et al. (37) also noted a definite increase in the redness of the retina and veins. The reduction in caliber of the vessels indicates a decreased blood flow, which they interpreted as a regulatory mechanism to protect the tissues from high oxygen concentrations. Despite this reduction in caliber, the color of the blood in the veins still approximated that of the arterioles. These observations indicate that, even with a slight arteriolar constriction, the tissues receive not only an adequate, but also an increased oxygen supply, as a result of the inhalation of 100% oxygen (94, 96). The same consideration holds true for other tissues, such as the brain (21).

Cornea and conjunctiva

It is generally accepted that the corneal epithelium utilizes atmospheric oxygen in metabolism (2). Bakker (10) doubts that
this source of oxygen is necessary to maintain a normal cornea. He enclosed intubated rats in a sealed chamber and exposed the corneas to high nitrogen concentrations for long periods. The corneas remained normal, indicating that they did not require oxygen from the ambient air to maintain their normal nutrition.

Comroe et al. (33) stated that 23% of their subjects developed conjunctival irritation after breathing oxygen at 760 mm Hg for 24 hours. This may be related to the irritative effect on serous membranes noted by other investigators (22, 27). It appears to be a direct effect of oxygen, and does not seem to be related to the humidity.

EFFECT OF OXYGEN ON IMMATURE RETINA

Retrolental fibroplasia is probably the most important retinal disease which can be classified as an intoxication (59). From the time that it was first described by Terry in 1942 (100) until its cause was established in the early fifties, it became the leading cause of blindness in preschool children. In spite of the fact that the toxicity of oxygen was well known (38), it took nearly ten years of intensive investigation to establish the etiology of this disease (14, 21, 35, 36, 53, 62, 64, 68, 83, 102).

In a large study, Kinsey (61) found that more than two-thirds of the premature infants subjected to routine oxygen (50% oxygen for 28 days) developed some active stage of retrolental fibroplasia, whereas less than one-third of those given oxygen only to meet acute clinical needs developed any stage of retrolental fibroplasia. Approximately 17% of the infants given routine oxygen developed cicatricial, or permanent forms of retrolental fibroplasia, compared with a 5% incidence in those who were limited to the actual need of oxygen. These facts clearly implicate prolonged exposure to high oxygen tensions as an important factor in the etiology of retrolental fibroplasia. Also significant is the finding that exposures to oxygen for periods of more than 3 weeks do not appreciably increase the incidence of disease, indicating once again a marked difference in individual tolerance to oxygen.
Oxygen is important in the vascularization process of the immature eye. Campbell (28) found that low atmospheric oxygen tension decreased the width of the capillary-free zone near the arteries. Ashton and Cook (6) found that the capillary-free zone of arteries was increased when the animal matured under hyperoxic conditions.

Other investigators have noted an initial vasoconstriction of the growing vessels, which progresses to complete obliteration if high oxygen concentrations are maintained (5, 8, 61).

Kinsey and Hemphill (63) have shown that the normal vascularization is suppressed in the immature animal's retina during exposure to high oxygen tensions. Subsequent vascularization may fail to develop normally. Gyllensten and Hellstrom (54) found the pathologic changes in mice were most severe in the youngest animals. Their animals developed vitreous and retinal hemorrhages, along with irregular proliferation of the nerve fiber vessels. Some eyes also showed atrophy of the ganglionic layer, inner nuclear layers, and outer plexiform layer. Patz et al. (81, 83, 84) also found vitreous degeneration, retinal edema, and localized retinal detachment in young animals exposed to 450 to 600 mm. Hg (60 to 80%) oxygen for 4 days or more. They stated that the oxygen-induced changes were limited to the eyes in his experiments.

In other studies, Ashton and Pedler (7) found that in the kitten's eye oxygen vaso-obliteration begins with capillary closure after only 6 hours' exposure, and is soon followed by degenerative changes in the endothelial cytoplasm. The degenerating cells are then moved from the affected capillaries toward less affected vessels, leaving only a thin strand of tissue. Finally, only a skeleton of the original vascular network remains. No changes were found in other retinal cells, even those adjacent to the endothelium. A single adult cat exposed in a similar manner showed no changes. These studies seem to indicate that oxygen toxicity acts primarily on a vascular basis, at least in the immature eye.

Ashton and Cook (6) were unable to produce changes in newly forming blood vessels in the rabbit ear under conditions of
hyperoxia. Moreover, hyperoxia does not seem to affect the growth of new vessels in standard lesions of the adult cornea (72). It can be concluded that the developing retinal vessels are uniquely sensitive to changes in oxygen tensions, and any alteration results in profound changes in the vascularization process.

Hellstrom (58) found no electroretinogram (ERG) changes on exposing kittens to oxygen, but kittens raised in high oxygen concentrations frequently developed an abnormal, "negative" ERG. Older kittens did not show the same sensitivity. These observations indicate an injury to the retina, which he thought could be explained either on the basis of ischemia caused by vaso-obliteration or by a direct cytotoxic effect of oxygen. Most of the abnormal ERG's tended to return to normal within a few weeks after the kittens were transferred to air.

In human infants, exposure to high oxygen concentrations results in immediate vasoconstriction. After 10 minutes the vessels dilate and remain dilated for about 6 hours. A delayed vaso-obliteration then occurs which is at first reversible by returning the individual to air, but later becomes irreversible. The vessel walls adhere to each other and degenerate. From this stage on, it makes little difference whether a high oxygen environment is maintained or not. Vessels immediately adjacent to the obliterated ones undergo vascular proliferation forming glomeruloid tufts. The newly formed capillaries invade the retina, penetrate the internal limiting membrane, and enter the vitreous. Retinal edema and subretinal exudate may lead to detachment. The detached retina organizes behind the lens, forming an opaque retro-lental mass which results in a white pupil (39, 66, 78, 79, 89, 90, 91). Subclinical cases may go unnoticed. Nauheim (75) attributes most cases of heterotopia of the macula to scarring and traction of the retina as a result of incomplete retrolental fibroplasia.

EFFECTS OF OXYGEN ON THE MATURE RETINA

The adult retina is extremely dependent on oxygen for normal function, and is the first organ to suffer from lack of oxygen.
Under hypoxic conditions, the retinal vessels dilate causing an increase in arterial pressure (47). There is a rapid reduction in visual fields, especially pronounced at low illuminations. The blind spot and angioscotoma, however, may be enlarged (49, 87) or reduced (22).

Brief hyperoxia at normal atmospheric pressures does not seem to have significant effect on vision. Miller (73) found no decrement in vision after breathing pure oxygen for 4 hours. Becker-Freyseng (13) noticed no decrease in dark adaptation while living in 90% oxygen for 60 hours, but performed no other visual studies. Harris et al. (56) found no decrement in tasks involving visual-auditory conflict while breathing oxygen. However, Behnke et al. (18) found that breathing oxygen at 3 atmospheres produced progressive contraction of the visual fields, dilation of the pupils, and some impairment of central vision after 4 hours. Normal vision returned within 1 hour after returning to a normal environment.

Rosenthal (95) noted a narrowing of the angioscotoma which occurred within 5 minutes of breathing oxygen at high tension and persisted as long as the oxygen was maintained. As soon as the oxygen was withdrawn, the angioscotomata dilated beyond their original width. These findings correspond quite well with the observed effects of oxygen on the retinal vessels.

The chronic effects of hyperoxia are less well studied, but may be more significant. Noell (76, 77) subjected adult rabbits to high oxygen concentrations for varying periods of time. Electroretinograms recorded throughout the experiment revealed reversible and irreversible changes throughout the pressure ranges studied. The irreversible effects were most extensive after exposure to high oxygen concentrations at ambient pressure. A significant attenuation of the b wave was manifest in 70% of the animals by the twenty-fifth hour of exposure to pure oxygen and was present in all by the thirty-sixth hour. By then the size of the b wave had declined to less than 30% of control. These changes were reversible to some extent when the animal was allowed to recover in normal atmosphere. On the average, recovery occurred only for those changes which had developed during the
last 6 to 10 hours of exposure. Irreversible effects of oxygen poisoning on the visual cells were observed with oxygen concentrations as low as 60% at ambient pressures.

Pathologic changes were seen on histologic sections from rabbits exposed to 100% oxygen for 40 hours. A major finding was the disappearance of most of the visual cells. The outer nuclear layer was reduced from a normal 4 or 5 rows to 1 or 2 rows of nuclei. Outer limbs were not recognizable, whereas some stumps of inner limbs still projected through the external limiting membrane from the visual cells which had survived.

These findings show a characteristic distribution in the retina. Vertical section through the eye shows that the most sensitive visual cells are located in the ventral half of the retina close to the central region. With prolonged exposure to oxygen, degeneration of the visual cells spreads from this region to other parts of the retina. Visual cells close to the ora serrata and optic nerve, however, usually survive.

In more recent studies, large, inflammatory retinal detachments, conjunctivitis, iritis, and hypotony have been produced in dogs within 48 hours in 760 mm Hg oxygen (15). These changes appeared to be largely reversible. The retina always reattached within one week. This reattachment was associated with the re-establishment of normal intraocular tensions. Several eyes showed retinal degenerative changes, however, that are associated with retinal detachment of long standing. The similarity of these lesions to those found in retrolental fibroplasia is interesting.

**SUMMARY**

The current interest in biomedical research, calling for human beings to be subjected to prolonged exposure to high oxygen environments, requires careful consideration of the possible hazards involved. A review of the literature clearly indicates that oxygen is capable of producing severe systemic toxicity. In the 1950's it was found that prolonged exposure to oxygen was responsible for retrolental fibroplasia in premature infants. Consideration of
the physiology of increased oxygen tensions of the eye shows that, as compared with other tissues, unusually high tensions may occur in the aqueous and vitreous. Experimental studies in many animals have revealed a variety of pathologic changes, some of which resemble those found in retrolental fibroplasia. Recent studies have found that these changes are not limited to immature animals. Investigators, working independently, have produced severe and irreversible changes in numerous mature, experimental animals. Careful consideration should therefore be given to the eye in any experiment involving prolonged exposure of human beings to high oxygen environments.

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