Effect of hyperbaric oxygenation on microcirculation: Use in therapy of retinal vascular disorders

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Recent advances in the use of high-pressure oxygen have led to renewed interest in the effects of hyperbaric oxygen on the retinal circulation and on retinal functions, especially in relation to therapy of ischemic conditions of the retina. In the study of the effects of oxygen toxicity, the influence of oxygen on the vision mechanism and on the development of retrolental fibroplasia hold very special interest, especially because recent studies indicate that irreversible ocular damage may occur in mature retinas after prolonged exposure to high partial pressures of oxygen.

The effect of oxygen on normal retina and retinal vessels

Retinal vessel caliber. Cusick, Benson, and Boothby found that anoxia induced in subjects breathing an oxygen-nitrogen mixture resulted in a dilatation of the retinal vessels, both arterioles and veins, amounting to an increase of from 10 to 20 per cent in their caliber. However, when such individuals were given pure oxygen at normal atmospheric pressure for 30 minutes, the caliber of the veins and of the arterioles was markedly diminished. The average diminution was 24 per cent for the arterioles and 28.2 per cent for the veins. Similar observations were made by other investigators. Saltzman and associates reported a clear response in the retinal vasculature, where marked vasoconstriction developed in direct relationship to the increase in arterial blood oxygen. It was found that hyperbaric oxygenation induced marked attenuation of both arterioles and venules, with complete elimination of the color differences between the veins and the arteries and the disappearance of the smaller retinal vessels. These changes were apparent during the first minute of oxygen respiration and reached a maximum within 5 minutes. Dollery and associates found
that hyperoxygenation induced vasoconstriction of the retinal vessels and postulated that this vasoconstriction was necessary in order to reduce the blood flow into the retina, which became hyperoxygenated.

Campbell and Hill, on the other hand, were unable to detect any change in the size of retinal vessels in subjects breathing pure oxygen for more than 5 minutes (the fundi were examined by Sir Stewart Duke-Elder).

**Visual acuity and fields.** Under hypoxia, in addition to the dilatation of the retinal vessels, there is marked reduction in the visual fields with enlargement of the blind spot. Brief hyperoxygenation at normal atmospheric pressure does not seem to have significant effect on vision or visual fields. Miller found no change in the visual acuity of subjects who had been breathing pure oxygen for 4 hours. The dark adaptation curves were not decreased while living in a 90 per cent oxygen atmosphere for 60 hours.

When oxygen was given at 3 atmospheric pressures, there was progressive contraction of the visual fields, with dilatation of the pupils and an impairment of central vision, beginning after 4 hours of administration of the oxygen. Yet these changes were reversible within that time limit because normal vision returned within 1 hour after returning to normal environment.

**Microcirculation.** Elgin noted that the arteriovenous oxygen difference was very low in the uveal tracts of dogs. He postulated that this indicated either shunting of blood through large capillaries in the ciliary processes or an increased skimming of blood, which propels only the liquid part of the blood and not the cells, to carry oxygen into the tissues via the small capillaries. However, the high level of oxygen in the venous side, which amounted to about 70 mm Hg, indicated that the gradient of physiologically dissolved oxygen in these capillaries would be advantageous for oxygen diffusion. When these dogs were given high oxygen for 30 minutes, their venous blood oxygen pressure was increased to an average of 252 mm Hg. This indicates that the gradient for physiologically dissolved oxygen from the capillaries to the cells, because of the previous low oxygen arteriovenous tension, would be one of the highest in the body.

The retinal vessels may behave in a similar way. According to Kuwabara and Cogan, blood oxygenation of the retina through the small capillaries is maintained by the mural cells of the retinal capillaries. These cells help maintain plasma skimming, thus preventing red cells from reaching the capillaries and permitting oxygen diffusion from the plasma alone.

In order to evaluate the effect of hyperbaric oxygenation on normal retinal function, studies similar to those of Kuwabara and Cogan using flat preparations of the retina and choroid are being made and correlated with studies on the differences in the arteriovenous oxygen tension. Furthermore, blood flow studies are being done on the choroid and the retinal circulation, studying the effect of hypoxia and hyperoxygenation in the animal, using scleral windows and microradioautography of retinal and choroidal flat preparations as methods of study.

**Toxic effects of oxygen**

**Immature retina.** The most important ocular intoxication with oxygen to date is retrolental fibroplasia, which between 1940 and the early fifties became the leading cause of blindness in preschool children. Since oxygen had been used routinely in newborn premature infants, oxygen toxicity and its relationship to the development of retrolental fibroplasia was gradually established. Kinsey found that it was not the time of exposure to oxygen that increased the incidence of the disease but rather the actual level of oxygen pressure used. He studied a large group of premature infants subjected to routine oxygen—as used at that time, i.e., 50 per cent oxygen for 28 days—and found that about two thirds of these infants developed various stages of retrolental fibroplasia. Yet in
a group of premature infants who were given oxygen only to meet their acute clinical needs, and never over 25 per cent, less than one third developed retrolental fibroplasia. Campbell found that, under low atmospheric oxygen tension, the width of the capillary-free zone near the arteries was decreased. Ashton and Cook found that this capillary-free zone was increased under hyperoxygenation. Continued hyperoxygenation induced an initial vasoconstriction of the growing vessels, which progressed to complete obliteration when hyperoxygenation was maintained. Thus normal vascularization appears to be suppressed in the immature animal's retina during exposure to high oxygen tensions.

Six hours after exposure to hyperoxygenation, degenerative changes in the endothelial cells of the retinal vessels were noted. Later these cells were replaced by strands of tissue, leaving behind only a skeleton of the original vascular network. Vitreous degeneration, retinal edema, and localized retinal detachment were also noted when such animals with immature retinas were exposed to 60 to 80 per cent of oxygen for 4 days or more. In the human infant, on the other hand, vasoconstriction is only transitory, since hyperoxygenation rapidly causes vasodilatation and only a delayed vasoobliteration occurs, which is reversible once oxygen tension is reduced. If oxygen administration is continued under high pressure, there is degeneration of the vessel walls, vascular obliteration, and subsequent neovascularization developing around the ischemic areas. These neovessels invade the retina and penetrate the internal limiting membrane into the vitreous. Retinal edema and subretinal exudates develop, leading to retinal detachment and retrolental cicatricial complications. Occasionally, when oxygen is stopped at the level of neovascularization, the process may be arrested.

**Mature retina.** Recent studies on the effect of hyperoxygenation on the retina showed that retinal detachment developed rather rapidly when dogs were subjected as short a time as 48 hours to pressures of oxygen varying between 680 and 760 mm. Hg. These dogs developed conjunctivitis, iritis, and hypotony, in addition. When the animals were removed from the oxygen tank for a few hours during the day, they could tolerate oxygen administration for longer periods of time—up to about 108 hours when removed for 3 to 6 hours daily. The retinal changes were those of multiple tiny punctate elevations, most easily seen over the tapetum. These gradually became confluent and coalesced and the detachment became larger and more complete. The vessels in the detached retina were seen to bend as they ran on the uneven surface. These retinas had no holes or tears. The tensions usually measured between 8 and 14 mm. Hg compared to the average normal for these dogs of 20 mm. Hg.

Hyperoxygenation may induce a decrease in the visual fields and visual acuity, even after 4 hours of administration. The electroretinograms in rabbits subjected to hyperoxygenation for varying periods of time revealed reversible and irreversible changes. The irreversible effects were most extensive after exposure to high oxygen tensions. Noell noted attenuation of the b wave when the animal was placed 25 hours or more in pure oxygen. This attenuation of the b wave became reversible when the animal was allowed to recover in normal atmosphere, and the recovery on the whole occurred within 6 to 10 hours of exposure. Hellström saw no electroretinographic changes in 2-week-old kittens placed in 85 to 90 per cent oxygen for 10 to 13 hours. Electroretinograms became abnormal, however, when such kittens were reared in 70 per cent oxygen for 3 to 4 weeks. Older kittens were not affected. These ERG changes were not aggravated by air and became normalized in a few weeks when the kittens were placed in air. Rabbits breathing oxygen for 40 hours or more showed disappearance of most of the visual cells. There was reduction in the outer nuclear layer. With prolonged exposure to oxygen, there was degeneration
of the visual cells spread from the central region to the periphery. Usually the visual cells close to the optic disc and the ora serrata survived last.\textsuperscript{1, 9-6}

**Hyperoxygen therapy of retinal anoxic disease**

**Retinal artery occlusion.** Carlisle, Lanphier, and Rahn\textsuperscript{38} used high oxygen inhalations in patients whose intraocular pressure was increased experimentally. They found that under normal conditions, when breathing normal atmospheric air, the visual acuity could not persist for more than 4 seconds. However, when these individuals were placed under 4 atmospheric oxygen, they could tolerate the “absolute” increase of intraocular pressure, i.e., intraocular pressure inducing no light perception, for over 50 seconds. Yet hyperbaric oxygen of less than 2 atmospheric pressures was of no avail. Patz\textsuperscript{39} used the inhalations of oxygen to treat 3 cases of retinal arterial occlusion. He claimed that after 3 minutes of administration of pure oxygen there was remarkable improvement in the visual acuity as well as visual fields of these patients. Anderson, Saltzman, and Heyman\textsuperscript{2} found no significant improvement in the treatment of retinal artery occlusion with hyperbaric oxygen. During the time of therapy, there was an increase in the arterial oxygen concentration in these patients, but they found marked vasoconstriction and not vasodilatation upon hyperbaric oxygenation. In one patient, during the therapy with oxygen, there was a slight increase in the visual fields under pressures of 300 to 400 mm Hg, but higher pressures of oxygen caused no improvement in the visual fields or vision. During therapy, the color of the veins approached that of the arteries and the retinal color also changed—there was disappearance of the cherry-red spot in one eye.

In our experience, hyperbaric oxygenation was used to treat 2 patients with central retinal artery occlusion. One patient (M. O.), during the therapy with hyperoxygenation, indicated that he had some light sensation in the temporal retina, yet following therapy vision remained at no light perception. There was no change in the size and color of the vessels even though the vessels of the normal eye became narrower and equal in color. The cherry-red spot in the macula did not change in size or color. The other patient (N. S.), who had partial central retinal artery occlusion with count-fingers vision, showed no improvement in visual fields or visual acuity after treatment with oxygen. Similarly, the retinal vessels in the affected eye did not change in size or color as the normal eye did. Following therapy, the patient saw everything blue with his affected eye, the visual sensation of blue spots almost filled the entire visual field, which thus appeared misleadingly full. In both of these patients, there was no vasoconstriction, but constriction was noted, as well as the approach of the color of the veins to that of the arterioles.

**Angioscotometry.** Angioscotoma was treated with hyperbaric oxygenation by Rosenthal,\textsuperscript{40} who found within 5 minutes of oxygen administration under high tension a narrowing of the angioscotoma which persisted as long as the oxygen was administered and returned to its original width as the oxygen was withdrawn. The pattern of the narrowing induced by oxygen inhalation, according to Rosenthal,\textsuperscript{40} followed that of the retinal vessels, which suggested that the effect was of peripheral rather than of central action of the oxygen.

**Central serous retinopathy.** Again, in our experience, one patient (A. S.) with central serous retinopathy, retinal edema with cherry-red spot, reduced visual acuity, and central scotoma was treated with hyperbaric oxygen. Under 2 atmospheres of oxygen and 100 per cent oxygen inhalation for 15 minutes, there was marked constriction of the arterioles and veins. The color of the veins approached that of the arterioles and so did the color of the retina. There was disappearance of the cherry-red spot, and the edematous retina looked very much like the rest of the retina and the retina in the
other eye. Immediately after withdrawal of oxygen, there was no change in the visual acuity, but there was a change in the relativity of the central scotoma. Again, this patient had a visual sensation of blue spots, as if stars, in the region of the central scotoma, which may have, again, mistakenly apparently reduced the boundaries of the scotoma. There was definite reduction in the scotoma, however, the day after therapy. After repeated treatment with hyperbaric oxygen at 3 atmospheres and 100 percent oxygen inhalation for 30 minutes, there was no change in the scotoma, yet the retinal changes were about the same.

Another patient (A. K.), with Paget's disease, angiod streaks, and marked exudative disciform macular retinopathy, was treated with hyperbaric oxygenation. There was no change in the visual acuity or the central scotoma, yet the patient developed increased loss of hearing. There had been an old middle ear disease. During oxygen administration, there was constriction of the arterioles and veins with similar changes in the color as noted in other patients. No change in visual acuity or fields was noted during or after treatment.

**Diabetic retinopathy.** Two patients with advanced diabetic retinopathy (J. A. and H. K.) were treated twice with hyperbaric oxygen under pressures varying between 2 and 3 atmospheres for periods of 1 hour each (the second period for H. K. had to be cut short because of intolerable earache during therapy, which subsided immediately after decompression). Both patients, and on each occasion, showed marked dilation of the arterioles during the treatment with oxygen, and the color of the veins approached that of the arteries. The veins were also dilated but to a lesser degree than the arterioles. In J. A., the arterial oxygen and CO$_2$ pressures were studied. At 2 atmospheres, pO$_2$ was 1,040 and pCO$_2$ 50 (pH 7.47), and at 3 atmospheres, pO$_2$ was 1,700 and pCO$_2$ 40 (pH 7.46).

A third patient (P. K.) with mild diabetic retinal changes showed under therapy with hyperoxygen no change in the retinal vessels either in size or color. None of the 3 patients demonstrated any appreciable change in visual acuity, retinal pathology, or visual fields.

**Conclusion**

Hyperbaric oxygenation may have an important physiopathologic role in ophtalmology in terms of its effect on the retinal functions, vascular and visual, and in terms of its toxic effects on the retina. In this presentation, the effects of hyperoxygenation in the treatment of such ischemic diseases which theoretically might benefit from hyperoxygenation were evaluated through our experience and that of others.

Contrary to the experience of Patz and of Anderson, Saltzman, and Heyman, our cases with central retinal artery occlusion did not show an appreciable change in the visual function of the affected retina. It was doubtful that the first patient (M. O.) did see the light in the temporal field of the affected eye. However, the experience of the second patient (N. S.), that of seeing blue, deserves further attention. There was no definite pattern to this blue visual sensation to support an entopic phenomenon. It is possible that this sensation is related to a dissociated effect of oxygenation on photoreceptors in the retina, which are more sensitive to the blue side of the spectrum. Noell suggested that the visual cells most susceptible to oxygen intoxication were those of the macular and equatorial areas, and the most resistant were those around the disc and the ora serrata. The patient with central serous retinopathy experienced such visual sensation of seeing blue spots, but only in the peripheral zones of his central scotoma. The effect of oxygen pressure on the central scotoma is interesting since the diminution in the central scotoma in our case occurred more dramatically with 2 and was not as pronounced with 3 atmospheric pressures.

In diabetic retinopathy, evidence seems to point out that the main abnormality is in the mural cells of the capillaries. If the oxygen metabolism in the retina or oxygen
diffusion to the retinal tissue—and for that matter, also the uveal tissue—is carried via one or both processes of blood shunting through a large network of capillaries and plasma skimming whereby red cells are excluded and, therefore, only the soluble part of oxygen is diffused through the small capillaries, one might anticipate that the use of oxygen might have some ameliorating effect on this disease. If oxygen-induced vasoconstriction is simply to shut off excessive oxygenation of the retina,\textsuperscript{10} then the vasodilatation noted in 2 of our cases with severe diabetic retinopathy may be related to an ischemic demand for oxygen. It certainly cannot be caused by oxygen toxicity, since in a case of mild diabetic retinopathy there was no vasodilatation noted. Furthermore, the oxygen arterial pressure in one patient (J. A.) was relatively low for both the 2 and the 3 atmospheres used in the therapy. The slight elevation of $p\text{CO}_2$, which may have resulted from hyperventilation during 100 per cent oxygen inhalation, could theoretically cause vasodilatation, since elevated $p\text{CO}_2$ does cause vasodilatation with air-breathing individuals. However, Saltzman and associates\textsuperscript{9} found that hypocapnia induced by hyperventilation while in hyperbaric oxygen and 100 per cent oxygen inhalation caused no change in the caliber of the vessels. If anything, a slight further diminution in the caliber was noted. Other explanations for this vasodilatation may be offered through studies of the arterial venous oxygen gradient in the microcirculation of diabetic patients, since in the normal uveal circulation, for instance, the gradient becomes one of the highest in the body because of the already high tension in the venous side.\textsuperscript{15} Any obstacle in oxygen diffusion, as caused by the suggested changes in the mural cells,\textsuperscript{10} would induce vasodilatation to improve mechanical diffusion by maintaining the gradient at higher level.

The use of hyperbaric oxygen in ophthalmology is still in its infancy. There is a lot more to learn about the dosage, i.e., the pressure, percentage, and duration of oxygen administration. Evaluation of fresh cases with retinal vascular accidents is most imperative before hyperoxygen therapy is condemned. Hyperoxygen therapy is certainly not the final solution for diabetic retinopathy, but the possibility that it may provide an unusual effect on the retinal vessels in this disease demands further exploration and evaluation.

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Appendix

Case reports.

Case 1. J. M. O., a 67-year-old white male, was treated in hyperbaric oxygen at 3 atmospheres for 1 hour with 100 per cent pure oxygen inhalation. During therapy, no change in the retinal vasculature was noted, and the macula remained cherry-red in color. Vision did not improve during therapy, even though the patient claimed an island of temporal light perception. The unaffected eye showed attenuation of the retinal vessels with equalization of the color of the arteries and veins. Following therapy, vision remained at no light perception. A second attempt at oxygen therapy failed because the patient developed sharp ear pain during compression.
Case 2. N. S. was a 71-year-old white male with a 1 week history of sudden painless blindness of the right eye followed by slow, very slight improvement in vision. Vision in the right eye was at count fingers at 2 meters. The fundus showed marked vascular attenuation with macular edema and pallor of the disc. The patient was treated with hyperbaric oxygen at 3 atmospheric pressures and 100 per cent oxygen inhalation for 1 hour. During therapy, there was no change in visual acuity. At the beginning of pressurization and at the end of decompression there were faint venous pulsations seen. The visual fields before and after therapy in the unaffected eye remained full, and so did the visual acuity. Following oxygen therapy, the patient saw all light in the affected eye in a blue hue. Thus, after therapy, visual fields were inadequate because of the bluish sensation, which mistakenly obliterated the central scotoma, especially toward the periphery.

Case 3. A. S., 41-year-old white male, had had the sudden onset of visual loss in the left eye of 1 month’s duration. Visual acuity in the left eye was 20/100, and the fundus showed marked edema of the posterior pole with cherry-red macula and yellowish small exudates. On visual fields, the patient had central scotoma. He was treated twice with hyperbaric oxygen—first in 2 atmospheres of pressure and 100 per cent oxygen inhalation for 15 minutes. During this time, there was moderate constriction of the retinal arteries with equalization of the color of both arteries and veins. The retinal color also changed. There was complete obliteration of the cherry-red color of the macula; the whole retina in the affected eye became as pink as that of the unaffected eye. During the treatment, there was no change in the visual acuity. Following therapy, visual acuity remained the same but the visual fields showed a decrease in the scotoma by about 10 degrees. Again, in the central scotoma, the patient experienced a bluish visual sensation, as if seeing stars at the periphery of the central scotoma, which may have mistakenly reduced the scotoma. However, 24 hours later, there was definite decrease in the central scotoma, which prompted a second treatment with hyperoxygenation.

This was given at 3 atmospheres of pressure and 100 per cent oxygen inhalation for 30 minutes. The fundus changes were about the same as during the previous therapy, but there was no change in the visual fields or in the visual acuity.

Case 4. A. K. was a 74-year-old white male who had Paget’s disease with angioid streaks and marked exudative discitis, without pain, bilaterally. The patient had count-finger vision in both eyes, with central scotoma in the left eye and central scotoma and infranasal segment field defect in the right eye. The patient was treated in hyperbaric oxygen at 3 atmospheres and 100 per cent oxygen inhalations for 45 minutes. There was marked attenuation of the blood vessels and equalization of the colors of both arteries and veins of the retina. However, there was no change in the visual acuity or the visual fields. The intraocular tension did not change during therapy with oxygen. Following therapy, the patient showed an increase in his hearing difficulty, which was the result of a previous middle-ear disease, which at the time of therapy with oxygen did not cause any difficulty.

Case 5. J. A., a 55-year-old white male, had had diabetes for 21 years and severe diabetic retinopathy for 1 year. Vision was count fingers with both eyes, and the fields were limited to a small paracentral island of vision. The patient was treated in the hyperbaric oxygen at 2 atmospheres, during which time there was dilatation of the arteries and, to a lesser extent, of the veins. When the pressure was increased to 3 atmospheres, there was sudden vas constrict for 5 minutes, followed by a dilatation which lasted until 1 minute after decompression. There was no change in visual acuity or in the visual fields. The patient was treated again in hyperbaric oxygen at 3 atmospheres and 100 per cent oxygen inhalations for 45 minutes. There was again an initial constriction followed by dilatation of the arteries. Again, there was no change in visual acuity or the visual fields. During therapy, arterial oxygen pressure was 1,040 mm., at 2 atmospheres and 1,700 at 3 atmospheres, which is relatively low (the normal for 2 atmospheres averages between 1,200, and for 3 atmospheres, ranges between 1,600 and 2,200). The CO2 arterial pressure was somewhat high at 2 atmospheres (50 mm.) but was close to the normal range at 3 atmospheres (40 mm.). The pH remained practically the same, at 2 and at 3 atmospheres, being 7.46 and 7.47, respectively.

Case 6. H. K., a 43-year-old white male, a known diabetic for many years, had a vitreous hemorrhage in the right eye and advanced diabetic retinopathy in the left eye. The vision in the right eye was hand motion and in the left eye was 20/50, with marked constriction of the visual fields. The patient was treated twice in hyperbaric oxygen. The first time, at 3 atmospheres and 100 per cent oxygen inhalation for 45 minutes, he had momentary initial constriction followed by dilatation of the arteries. His visual acuity and fields were not affected. Therapy was repeated, but because of sharp earache, decompression was necessary. During the time he was in hyperoxygen, there was no change in the visual fields or visual acuity.

Case 7. D. K., a 52-year-old white female, who was known to be diabetic, had minimal vascular changes in the retina. Her vision was 20/20 in
both eyes. She was placed in the hyperbaric oxygen at 3 atmospheres with 100 per cent oxygen inhalation for 45 minutes. There was no appreciable change in the vasculature of either eye, even though the color of the veins equaled that of the arteries. Visual fields and visual acuity before and after treatment in the hyperbaric oxygen did not change appreciably.