We reviewed research on retinal oxygen (O₂) distribution and use, focusing on O₂ microelectrode studies in animals with circulatory patterns similar to those of humans. The inner and outer halves of the retina are different domains in terms of O₂. Understanding their properties can suggest mechanisms of and therapies for retinal diseases. Inner retinal PO₂ averages about 20 mm Hg. Effective O₂ autoregulation of the retinal circulation ensures that inner retinal PO₂ is relatively uninfluenced by systemic hypoxia and hyperoxia and increased intraocular pressure in healthy animals. Failures of the retinal circulation lead to tissue hypoxia that underlies the vasoproliferation in diabetic retinopathy and retinopathy of prematurity. Choroidal blood flow is not regulated metabolically, so systemic hypoxia and elevated intraocular pressure lead to decreases in choroidal PO₂ and photoreceptor O₂ consumption. The same lack of regulation allows choroidal PO₂ to increase dramatically during hyperoxia, offering the potential for O₂ to be used therapeutically in retinal vascular occlusive diseases and retinal detachment.

Oxygen (O₂) is essential for retinal function. As in other tissues, O₂ diffuses through the tissue passively from the circulation and is consumed in the oxidative production of adenosine triphosphate. However, several features make retinal oxygenation unique, and these have an impact on the pathogenesis and treatment of retinal diseases. Among the unique features influencing retinal oxygenation are the presence of a dual circulation, lack of metabolic regulation of the choroid, presence of O₂ regulation of the retinal circulation, and localization of mitochondria to photoreceptor inner segments. In most cases, it is useful to think of the retina as the following 2 domains: the avascular outer retina and the vascularized inner retina. The retina is also one of the most metabolically active tissues, consuming O₂ more rapidly than many other tissues, including the brain. Because the demand for O₂ is high, and because it cannot be stored in the retina or other tissues, a continuous O₂ supply is essential. This review focuses on vascularized retinas (eg, of the rat, cat, pig, monkey, and human) in which O₂ is delivered by the retinal and choroidal circulations. In some species, retinal vasculature is nearly or completely absent (eg, the rabbit and guinea pig). These retinas rely on the choroid almost exclusively and the inner retina is strongly glycolytic. A review focusing on avascular and partially vascularized retina has been presented elsewhere.

Retinal O₂ tension (PO₂) and other variables that provide an index of PO₂ have been measured in several ways, which have recently been presented by Hogeboom van Buggenum et al. Hemoglobin saturation in retinal vessels has been measured by several groups. Intravascular PO₂ has been measured with a phosphorescent dye, for which decay is inversely proportional to the PO₂. Berkowitz and coworkers have pioneered the development of magnetic resonance imaging techniques that measure absolute PO₂ in the preretinal vitreous.

From the Departments of Biomedical Engineering (Drs Wangsa-Wirawan and Linsenmeier) and Neurobiology and Physiology (Dr Linsenmeier) and the Institute for Neuroscience (Dr Linsenmeier), Northwestern University, Evanston, Ill. The authors have no relevant financial interest in this article.
Trode O2 consumption (QO2) is about the same as that in the position of the intraretinal electrode.21,22 The invasive nature of the microelectrode is the major disadvantage of this technique, because the electrode may damage the tissue during measurement. Hence, this technique has limited clinical application. To date, microelectrodes have only been used in humans to measure O2 in the vitreous during intraocular surgery.23,24 Some authors have argued that O2 consumption by the microelectrode itself is another disadvantage.12 However, small microelectrodes have been able to map out O2 gradients within the retina with high spatial and temporal resolution. We will focus on these measurements in the first part of this review. In some of this work, a second barrel of the electrode has been used to record the local electroretinogram and the transepithelial potential across the retinal pigment epithelium. The copper wire from the other barrel is connected to a picoammeter to measure currents proportional to PO2.

Figure 1. Schematic diagram of intraretinal oxygen measurements. A double-barreled microelectrode is used as described elsewhere by Linsenmeier and Yancey20 and inserted into the vitreous through a 15-gauge needle mounted onto a manipulator that allows gonioscopic motion. A boot system is installed to maintain intraocular pressure and to prevent vitreal leakage. The microelectrode is then connected to a microdrive that controls movement in and out of the retina. One barrel, filled with isotonic sodium chloride solution and connected to an amplifier via a silver/silver chloride (Ag/AgCl) wire, measures voltages generated in the retina (the intraretinal electoretinogram and the transepithelial potential across the retinal pigment epithelium). The copper wire from the other barrel is connected to a polarizing voltage (−0.7 V) and a picoammeter to measure currents proportional to PO2.

Figure 2. Intraretinal oxygen profiles across cat retina during light and dark adaptations. The retina is shown schematically at the top. The 4 cell types shown are (from left to right) retinal pigment epithelial cells, rod photoreceptors, bipolar cells, and ganglion cells.

The normal O2 profile in light and dark

Outer Retina

In vivo O2 profiles have been recorded from pigs,21,32 cats,22,33 rats,34 and monkeys.35 These studies have shown similar O2 profiles everywhere except in the monkey fovea. Under light-adapted conditions (ie, enough light to saturate rod responses), the PO2 falls steeply between the choriocapillaris (approximately 60 mm Hg) and the photoreceptor inner segments and subsequently decreases more gradually through the outer retina, as shown in Figure 2. The direction of this gradient indicates that all of the O2 used by the photoreceptors comes from the choroid under light-adapted conditions. In darkness, the PO2 in the outer retina is considerably lower,22,35 reaching 0 mm Hg at the proximal side of the inner segments. Sometimes much of the outer nuclear layer in the cat has a PO2 of 0 mm Hg (Figure 2). This low value leads to a reversal of the gradient of O2 proximal to the inner segment, so that in darkness, O2 also diffuses from the retinal circulation to the photoreceptors.

The steep drop of PO2 from the choroid reflects the high rate of O2 use by the photoreceptors.36,37 The high choroidal PO2 is maintained by the unusually high flow rate in the choroidal circulation.38-40 which is necessary for providing enough O2 to the retina.41
Inner Retina

One or more O2 peaks appear in the inner retina (Figure 2). These indicate O2 sources and, therefore, the presence of nearby retinal vessels. The preretinal PO2 in the vitreous is normally a good indicator of inner retinal PO2,42,43 because the vitreous consumes very little O2,44 and the inner retina is the source of vitreal O2.43,44 The average PO2 in the inner retina of the cat during dark adaptation was 18.5 mm Hg,45 which is in good agreement with the preretinal PO2 in cats of 18.9,28 20 to 30,44 15 to 20,42 20.2,33 and 19 mm Hg.46 The similarity of retinal and vitreous P O2 may break down under some conditions, however, including diabetes mellitus.47

The values of inner retinal PO2 cover a relatively wide range (Figure 3). The average PO2 is a few millimeters of mercury lower in light adaptation.22,45 The O2 extraction from the retinal circulation is high relative to that in many tissues, about 8 mL O2 per 100 mL blood,10 resulting in a low venous PO2 that contributes to making the average tissue PO2 in the retina lower than in many organs.68

OXYGEN METABOLISM

Oxygen consumption can be derived from material balances in vivo from blood arteriovenous differences49,50 or in vitro from reductions in PO2 in a closed chamber.3,31,32 Oxygen consumption can also be obtained by fitting mathematical models of O2 diffusion and consumption to PO2 profiles.22,26,53 The use of material balances does not provide information on the spatial distribution of consumption, but was the first method to show that QO2 was higher during dark than light adaptation in the whole retina.32,44 Further aspects of retinal energy metabolism, particularly the unusual amount of glycolytic metabolism, have been reviewed recently.3,55

Outer Retina

Absolute values of photoreceptor QO2 were computed by fitting a mathematical model of O2 diffusion in the outer retina to the O2 profiles.33 In the most satisfactory model, all the O2 use is confined to the inner segment layer. It is important to realize that even though QO2 is negligible in the outer segment and outer nuclear layers, linear gradients of O2 still remain throughout these regions (Figure 2, Figure 4, and Figure 5). The evidence of a non-zero QO2 is not the presence of a gradient but curvature in the profile, specifically a quadratic dependence of PO2 on distance.55

The Table shows that QO2 of the photoreceptors during steady illumination is 36% to 68% of the value in the dark. This agrees with the effect of light found by other methods in the rat, rabbit, and pig.9,36,58 Above rod saturation, which is below-normal room illumination, no further changes in QO2 are observed in the rod-dominated area centralis of the cat retina.25 Modeling also shows that the choroid is essential to photoreceptor metabolism, contributing approximately 90% of the O2 consumed by the photoreceptors in darkness, and all of the O2 consumed

![Figure 3. Frequency histogram of the distribution of inner retinal PO2 in dark adaptation.](https://archopht.jamanetwork.com/fullarticle/121/4/549/Figure3.png)

![Figure 4. Intraretinal oxygen profiles recorded in dark during normoxia and hypoxemia.](https://archopht.jamanetwork.com/fullarticle/121/4/549/Figure4.png)

![Figure 5. Intraretinal oxygen profiles in dark during normoxia and hyperoxia.](https://archopht.jamanetwork.com/fullarticle/121/4/549/Figure5.png)
Oxygen Consumption Rate Measured From Animals With Vascular Retinas, During Dark and Light Adaptation in Outer and Inner Retina*

<table>
<thead>
<tr>
<th>Dark</th>
<th>Light</th>
<th>Subject</th>
<th>Reference (Year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outer retina</td>
<td>3.7</td>
<td>2.3</td>
<td>Rats</td>
</tr>
<tr>
<td></td>
<td>3.9</td>
<td>1.4</td>
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<td>4.4</td>
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<td>Cats</td>
</tr>
<tr>
<td></td>
<td>4.9</td>
<td>2.6</td>
<td>Cats</td>
</tr>
<tr>
<td>Inner retina</td>
<td>3.5</td>
<td>2.4</td>
<td>Monkeys</td>
</tr>
<tr>
<td></td>
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<td>Rats</td>
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<tr>
<td></td>
<td>3.5</td>
<td>3.7</td>
<td>Cats</td>
</tr>
</tbody>
</table>

*Data are expressed in milliliters of oxygen per 100 g of tissue per minute.

During light adaptation, the choroid contributes approximately 50% of the O₂ consumed by the whole retina in dark adaptation, which is consistent with earlier estimates based on choroidal arteriovenous O₂ differences and blood flow. The Table gives values for O₂ as though the consumption were uniform across the whole outer retina. We have preferred to report the values this way, because it reduces the scatter in the measurements and makes values from modeling more comparable to those obtained by other methods. These values are somewhat misleading, however, since the O₂ is localized to the inner segments. The rod inner segments have an extremely high O₂ of 15 to 20 mL O₂ (standard temperature and pressure) per 100 g of tissue per minute in the dark, consistent with the high density of mitochondria in this region. Little is known about cone O₂. Light does decrease the O₂ of monkey fovea. Cones in the monkey have a volume of mitochondria that is about 10 times that of rods, but we have argued that O₂ of an individual cone could not be higher than that of a rod by a factor of 10, because the smaller number of mitochondria in rods already uses all the O₂ available from the circulation. Oxygen is used in photoreceptors for many processes, but the ones that appear to require the most energy are maintenance of the dark current, ie, pumping out the large load of sodium ion that enters through the light-dependent channels and generating guanosine triphosphate, from which cyclic guanosine monophosphate is produced. The dark current decreases dramatically during illumination, whereas the guanosine triphosphate turnover increases. These appear to be the only processes whose metabolic demands change significantly with illumination. The change in sodium ion pumping is larger, however, and, as a result, illumination causes a net decrease in photoreceptor O₂.

In the inner retina, the retinal circulation forms a 3-dimensional mesh, which makes mathematical modeling difficult. The retinal circulation must be occluded to allow the application of a diffusion model to the inner retina. Despite this limitation, various lines of evidence indicate that in the inner retina, no difference in QO₂ exists between darkness and steady illumination (Table). The metabolism of the inner retina is higher when flickered light (4 Hz) is applied as opposed to steady light, presumably because flickered light leads to greater neural activation. Unfortunately, this increase is difficult to quantify.

**RETIINAL OXYGENATION UNDER ALTERED CONDITIONS**

**Hypoxemia**

Figure 3 shows intraretinal O₂ profiles from the dark-adapted cat retina during normoxia and hypoxemia, induced by adding nitrogen to the inspired gas. In the inner retina, tissue O₂ is effectively regulated across a wide range of PaO₂. The decrease in preretinal PO₂ is only 0.14 to 0.18 mm Hg/mm Hg PaO₂ when the PaO₂ is above 35 mm Hg in the cat, and 0.2 mm Hg/mm Hg PaO₂ in the miniature pig. When the PaO₂ falls below 35 mm Hg, PO₂ in the inner retina decreases more steeply, approximately 0.62 mm Hg/mm Hg PaO₂. The good regulation at PaO₂ of greater than 35 mm Hg results from vasodilation of the retinal circulation, which in cats can increase blood flow by more than a factor of 3 during hypoxemia.

In the outer retina, hypoxemia leads to a steep decrease in choroidal PO₂ (Figure 4) of approximately 0.64 mm Hg/mm Hg PaO₂. This occurs because the choroidal blood flow does not increase in hypoxemia (Melissa Pulfer, Jameel Ahmed, PhD, and R.A.L., unpublished data, June 2000). There would be little advantage of increasing choroidal blood flow, even if this were possible. The usual advantage of increasing blood flow to a tissue during hypoxemia is allowing the arteriovenous O₂ difference to be reduced, which minimizes or prevents a decrease in venous PO₂ during hypoxemia. In the choroid, the arteriovenous O₂ difference is already very small, only about 1 volume percent, due to the high rate of blood flow. In relatively mild hypoxemia, arterial PO₂ drops below the normoxic choroidal venous PO₂. Reducing the arteriovenous difference could not prevent this. Because photoreceptor metabolism is O₂ limited under normoxic conditions in darkness, even mild hypoxemia (PaO₂ of 60 mm Hg) reduces the flux of O₂ to the inner segments and, therefore, reduces photoreceptor QO₂. When hypoxemia occurs during light adaptation, choroidal PO₂ also falls, but in this case, metabolism is not O₂ limited, so photoreceptor QO₂ is not affected.

**Elevated Intraocular Pressure**

When the intraocular pressure (IOP) is elevated, the effects on retinal PO₂ are similar to those observed during hypoxemia. Decreased perfusion pressure does not affect PO₂ in the inner retina owing to effective autoregulation in the retinal circulation. In contrast, when the IOP is elevated, the choroidal blood flow decreases, which leads to a reduction of choroidal PO₂ of approximately 0.5 mm Hg/mm Hg of perfusion pressure. This reduction leads to a reduction in photoreceptor QO₂. An extension of this finding is that anything that decreases choroidal blood flow would be...
expected to have a negative impact on retinal oxygenation and on photoreceptors. There is evidence that human and experimental glaucomas affect photoreceptors, possibly because they reduce photoreceptor O₂ supply, and there is direct evidence of retinal damage by reduced choroidal blood flow in birds.

**Hyperoxia**

Figure 5 compares a normoxic profile to one obtained during hyperoxia (inspiration of 100% O₂). Vitreal O₂ and inner retinal O₂ are well regulated during hyperoxia in the cat, pig, and rat and presumably in humans. This regulation is due to constriction of retinal vessels and reduction of retinal blood flow. In the miniature pig, PO₂ in the inner retina has been reported to be perfectly regulated during hyperoxia in intervascular zones, but it increases by an average of approximately 40 mm Hg in juxta-arteriolar zones, the same value observed in cats. Adding 5% carbon dioxide to the inspired gas leads to larger increases in inner retinal PO₂ during hyperoxia. The most striking change during hyperoxia is the increase in choroidal PO₂ to about 250 mm Hg in cats and 220 mm Hg in miniature pigs. This increase is a consequence of the lack of metabolic regulation of choroidal blood flow.

It is sometimes thought that hyperoxic therapy has a limited potential for treating retinal disease. This is based on the idea that the blood is nearly saturated with O₂ during normoxia, so that the small additional O₂ content during hyperoxia should be of little benefit. The fundamental misconception is that the O₂ supply to the tissue relies on O₂ saturation, whereas, in reality, O₂ moves into tissue by simple diffusion, which is driven by gradients of PO₂, not saturation. The PO₂ gradient from the choroid is much steeper during hyperoxia, and a greater portion of the retina can be supplied by the choroid during hyperoxia than during normoxia as shown in Figure 5.

Despite an abundance of O₂, higher photoreceptor QO₂ was not found in cat retina during hyperoxia. Pournaras and coworkers argued that QO₂ increased during hyperoxia in healthy retinas of the miniature pig, but not in retinas with a branch vein occlusion. Their conclusions were not based on calculations of QO₂, however, but only on the steepness of gradients, which cannot be used to infer values for QO₂. The gradient through the outer segments is steeper during hyperoxia, so the flux across them is larger, but they never use any O₂.

For a few hours, at least, hyperoxia does not impair retinal electrical function in animals, but the issue of O₂ toxicity to the retina has not been fully addressed. It is clear that O₂ can be damaging to photoreceptors if combined with high levels of illumination.

**Clinical Issues**

**Diabetic Retinopathy**

Diabetic retinopathy is a disease predominantly of the retinal vasculature, leading first to capillary occlusion and then to vascular proliferation. For many years, tissue hypoxia has been suggested to be involved in the progression of diabetic retinopathy and retinal neovascularization in general. By the time that capillary nonperfusion is clinically observable, tissue hypoxia has likely occurred, but the exact time when hypoxia begins is as yet unknown. Retinal tissue hypoxia was not found in the early stage of diabetic retinopathy in animal models. However, intraretinal O₂ measurements on cats with long-term (6-7 years) diabetes mellitus showed an abnormally low average inner retinal PO₂ of 7.7 mm Hg (compared with 16.4 mm Hg in normal cats). This report, the only one to provide intraretinal measurements, stressed that tissue hypoxia was present in the diabetic retina before capillary dropout was evident and when only a few microaneurysms were present. Further evidence of hypoxia relatively early in the disease was provided by the observation that hyperoxia reversed early contrast sensitivity deficits and oscillatory potential reductions.

In addition, Arden et al provided evidence of altered dark adaptation in diabetes mellitus, which was also suggested to be an effect of hypoxia.

Hypoxia may occur during diabetic retinopathy due to capillary occlusion. Leukocytes have been reported to be present in greater number and are less deformable in diabetic cats. Increased levels of endothelial cell/leukocyte adhesion molecules (intercellular adhesion molecule 1 and P-selectin) have been also observed in humans with diabetes mellitus (hereafter referred to as diabetic humans). These findings may explain the increase of leukocyte activation and adhesion in diabetic humans and rats, which are known to increase vascular resistance as capillaries become plugged. In addition, a hyperglycemic (hyperosmotic) environment increases the adhesion of leukocytes to retinal endothelial cells.

The findings of tissue hypoxia and occlusion of retinal capillaries by leukocytes are consistent with observations that retinal blood flow is reduced before and in the early stages of diabetic retinopathy. A subsequent increase in retinal blood flow occurs, possibly because lower-resistance shunt pathways develop and carry some of the flow and because vascular endothelial growth factor (VEGF) dilates vessels. The flow is reduced again in proliferative retinopathy. Complete consensus on this sequence of events has not been achieved, but they seem to explain most of the observations.

One of the puzzles about diabetic retinopathy has always been why it affects the microvasculature of the retina more than that of the brain. Arden et al suggested that dark adaptation aggravates hypoxia by depriving the inner retina of the small amount of O₂ that diffuses from the choroid during light adaptation. They suggested further that avoiding a long period of dark adaptation (eg, during sleeping at night) could be an alternative therapy for diabetic retinopathy.

Hypoxia is thought to induce the synthesis of VEGF, which is present in higher levels during proliferative diabetic retinopathy. Vascular endothelial growth factor has also been found in eyes with no retinopathy or only early signs of retinopathy. This initially suggested that factors besides hypoxia may induce the production of VEGF, but we now know that the retina is hypoxic early in the disease. Although VEGF...
is important, other angiogenic factors may also be involved. A detailed discussion on factors involved in intraretinal neovascularization is available elsewhere. A competing theory of vasoproliferation implicated the mechanical aspect of vasodilation resulting from hypoxia or hyperglycemia. This theory has received little attention recently, but it seems prudent to recognize that mechanical factors could play a role in angiogenesis.

The \( Q_{O2} \) of the retina in diabetes mellitus has been a subject of controversy. In the intact cat retina, photoreceptor \( Q_{O2} \) was lower on average in subjects with diabetes than in healthy subjects, but \( Q_{O2} \) has a strong positive correlation with choroidal \( P_{O2} \), and the choroidal \( P_{O2} \) values tended to be lower in diabetic cats. Whether lower choroidal \( P_{O2} \) is a general feature in diabetes could not be determined with the number of animals available in that study. In vitro studies in rabbits suggested that the \( Q_{O2} \) decreased in diabetes. In contrast, one study reported that \( Q_{O2} \) in diabetic rats was greater. Little work has been done on the \( Q_{O2} \) of the inner retina. Tiedeman et al. found that retinal venous \( P_{O2} \) saturation was lower than in normal diabetic humans, and concluded on that basis that \( Q_{O2} \) of the inner retina must be greater in subjects with diabetes. If blood flow increased or was unchanged, this would be a reasonable conclusion, but blood flow was not measured in that study. Increased \( Q_{O2} \) is difficult to reconcile with capillary dropout and inner retinal damage.

On the theory that one of the major problems in diabetic retinopathy is lack of \( O_2 \) in the inner retina, therapies have been designed to improve the \( O_2 \) supply. Panretinal photocoagulation is effective in treating proliferative retinopathy. Studies on animal models and in humans showed that \( P_{O2} \) in the preretinal vitreous is higher over photocoagulated regions than over normal regions. These measurements provided little detail about \( O_2 \) gradients in the retina, and were obtained mainly during hyperoxia, which is not the condition in which diabetic retinopathy develops or progresses. Nevertheless, they provide some evidence that photocoagulation reduces the \( Q_{O2} \) of the photoreceptors, allowing more \( O_2 \) to diffuse from the choroid to the inner retina.

Retinal damage from ischemia can be reversed if early retinal circulatory changes preceding VEGF upregulation are detected early. An attempt to delay the development of ROP by minimizing auto-oxidative reactions that arrest the growth of normal blood vessels is promising in non-human primates. Other therapies, such as gradual reduction in \( O_2 \) level (oxygen weaning) appear less promising.

Mechanistically, the disease is not as straightforward as the above discussion would suggest. As in diabetic retinopathy, it has been impossible to determine exactly what the oxygenation status of the human retina is at any time during the disease progression, and difficult even in the animal models. More recently, attention has shifted to a rodent model of ROP called ischemia-induced or \( O_2 \)-induced retinopathy. Retinopathy is produced most effectively by a regimen that cycles the inspired gas between a relatively hypoxic one and a relatively normoxic one for at least several days during retinal vascular maturation. Surprisingly, well-controlled hyperoxia followed by normoxia produces ROP-like symptoms with less certainty than does \( O_2 \) cycling. In \( O_2 \)-induced retinopathy, some evidence from novel magnetic resonance imaging measurements suggests that hypoxia plays a role early in the disease. This conclusion is based on a blunted response of retinal oxygenation to breathing of carbogen (a mixture of 95% \( O_2 \) and 5% carbon dioxide) in animals in which histological signs of the disease developed, rather than a direct demonstration of tissue hypoxia.

As in diabetic retinopathy, it is thought that hypoxia does not directly affect vessel growth, but instead influences the production of angiogenic factors in the retina with the probable involvement of hypoxia-inducible factor 1 as an intermediate.

Vascular Occlusive Diseases

Work on complete ocular ischemia, produced in general with elevation of IOP, and work on the effects of anoxia on the retina in vitro have a long history. Although they are relevant to ocular ischemic syndrome, in which the retinal and choroidal circulations are compromised by carotid artery obstruction, they will not be reviewed herein. Of more interest from a clinical standpoint is the role of \( O_2 \) in central and branch venous and arterial occlusions of the retinal circulation. Experimental venous occlusion in pigs leads to decreased inner retinal \( P_{O2} \), which can be followed by neovascularization. Work on cats shows that retinal arterial occlusion makes the entire inner retina anoxic, and this causes a rapid failure of the ERG b wave.
in cats and monkeys. Even when the animal breathes air, the retina is reasonably tolerant to occlusion, surviving episodes of 100 to 120 minutes with full recovery of the ERG after the occlusion is reversed. Several studies have shown that retinal oxygenation can be partially or completely restored during the arterial occlusion by making animals hyperoxic. It is clear from O₂ profiles that this effect relies on an increased O₂ supply from the choroid during hyperoxia. Corroborating the importance of O₂ as the limiting factor during occlusion are a few studies that have used a model of total ischemia. Anderson and Saltzman have shown that if human subjects breathed O₂ before IOP elevation, their vision was sustained longer than if they breathed air. Blair and coworkers have shown that perfusing the vitreous with an oxygenated solution after total occlusion can maintain the structural integrity of the retina and the ERG. Despite this positive experimental data, the clinical experience with hyperoxia has been mixed, with only a few studies recommending hyperoxia as a treatment for vascular occlusion. Unfortunately, most clinical attempts to provide hyperoxia during occlusion have not adequately considered that it must be provided for large blocks of time and as soon as possible because O₂ is not stored and is used so rapidly. In addition, there have been two fears of using hypoxic therapy. First, hyperoxia constricts retinal vessels, and this might impede the clearance of emboli. This may be an unnecessary concern, because the inner retina is acidic during occlusion (Gulnur Birol, PhD, N.D.W.-W., Ewa Budzynski, MS, and R.A.L., unpublished data, October 2002), which would tend to counteract hyperoxic vasoconstriction. In addition, carbon dioxide can be added to the inspired gas to induce vasodilation. Second, extended O₂ breathing can be toxic, but this should not prevent hypoxic therapy, because it is possible to breathe 60% to 70% O₂ for hours without toxic effects.

Other Diseases

Oxygen undoubtedly plays a role in other diseases. Several studies report that cystoid macular edema can be ameliorated by hyperbaric O₂ therapy. No clear theoretical reason for this exists. Depending on the mechanism of this effect, hyperoxia at normal atmospheric pressure may do just as well. This has not been tested, but should be, because it would allow application of the therapy to more patients.

Oxygen is likely to play a role in the dramatic vasoattenuation of the retinal circulation that is associated with photoreceptor degenerations in humans and animals. This role can be understood on the basis of the normal gradients. When photoreceptors are lost, O₂ derived from the choroid that was once used by photoreceptors now diffuses all the way to the inner retina. In addition to the reduced size of the major vessels, capillaries in the inner retina are permanently lost in animals with photoreceptor degeneration. This capillary loss can be prevented by maintaining the animals under hypoxic conditions, which probably reduce the flux of O₂ from the choroid to the inner retina. Evidence also exists that O₂ can modulate the survival of photoreceptors early in the Royal College of Surgeons rat model of retinal degeneration. Hyperoxia is protective at early stages, whereas hypoxia induces death of photoreceptors. Up-regulation of basic fibroblast growth factor by hypoxia is not sufficient to prevent photoreceptor death, and later stages of the photoreceptor loss may not be caused by hypoxia.

Although a focus on mechanical causes of ganglion cell loss in glaucoma continues, many lines of evidence indicate that reduced ocular blood flow, and by implication reduced O₂, is a contributing factor in the retinal damage in glaucoma. This is a complex area in which most of the evidence is indirect, but support for a vascular hypothesis continues to accumulate. First, hyperbaric O₂, which does not change IOP, can improve visual fields in glaucomatous subjects. Second, photocoagulation, which destroys photoreceptors and presumably increases the inner retinal O₂ supply from the choroid, promotes survival of ganglion cells in glaucomatous monkeys. Third, cones, which should not be affected directly by mechanical stresses at the optic nerve, are swollen in eyes of humans with glaucoma and in primates with experimental glaucoma. Finally, systemic vascular variables, which have been known to be risk factors for glaucoma, help predict the degree of visual dysfunction in glaucoma.

Oxygen may also play a role in vision loss in retinal detachment. A recent argument has been made on a theoretical basis that hyperoxia may be useful in preventing photoreceptor damage. Detachment separates the inner segments from their O₂ supply, and although no consuming tissue is found under the retina, the increased distance reduces the flux of O₂ from the choroid to the photoreceptor inner segments. Hyperoxia should restore this flux, at least for detachments of moderate height, because increased choroidal PO₂ can compensate for the increased distance. For large detachments, the photoreceptors may benefit more from increased amounts of O₂ in the retinal circulation than in the choroidal circulation. The protective effect of hyperoxia on detached photoreceptors has been shown experimentally in cats, in which hyperoxia was able to save photoreceptors and prevent the activation of retinal glia normally caused by detachment.

CONCLUSIONS

Most of the important features of normal retinal oxygenation are now known, and the status of retinal oxygenation in some prevalent diseases has been partially elucidated. Tissue hypoxia is believed to be important in regulating vascular growth factors, particularly in the vasoproliferation observed in diabetes mellitus and ROP. Hypoxia is also involved in the loss of photoreceptors during a retinal detachment and the loss of inner retinal neurons in retinal arterial occlusions. Evidence is emerging that hypoxia may damage photoreceptors and possibly other cells in glaucoma, and that O₂ modulates the survival of photoreceptors in photoreceptor degenerations. One of the most interesting aspects of retinal oxygenation is the important metabolic role of the choroidal circulation. Lack of regulation of the choroid by O₂ may be detrimental to the photoreceptors under conditions when choroidal PO₂ or choroidal blood flow decrease (eg, glau-
coma), but this same lack of regulation provides an opportunity to use the choroidal therapeutically in treating cystoid macular edema, retinal arterial occlusions, and retinal detachment. Oxygen therapy only has a chance of working if it is sustained, however, and this has generally not been the mode in which it has been used.

The difficulty of measuring O₂ intraocularly in humans or in animal models of human diseases has prevented a more complete understanding of the role of O₂ in retinal diseases. Measuring retinal O₂ would be far better than measuring blood flow, because tissue PO₂ is the variable that is directly relevant to metabolism and presumably to visual function. Noninvasive measurements have been difficult, because of the spatial heterogeneity of PO₂ in the retina and the difficulty of accessing the choroid, but these techniques are important and need to be developed. Development of noninvasive optical techniques would allow one to study the timing of hypoxia with respect to biochemical and histological changes, and would serve as a way to follow disease progression and evaluate treatments.

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