

Retinal Oximetry Discovers Novel Biomarkers in Retinal and Brain Diseases

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PURPOSE. Biomarkers for several eye and brain diseases are reviewed, where retinal oximetry may help confirm diagnosis or measure severity of disease. These include diabetic retinopathy, central retinal vein occlusion (CRVO), retinitis pigmentosa, glaucoma, and Alzheimer's disease.

METHODS. Retinal oximetry is based on spectrophotometric fundus imaging and measures oxygen saturation in retinal arterioles and venules in a noninvasive, quick, safe manner. Retinal oximetry detects changes in oxygen metabolism, including those that result from ischemia or atrophy.

RESULTS. In diabetic retinopathy, venous oxygen saturation increases and arteriovenous difference decreases. Both correlate with diabetic retinopathy severity as conventionally classified on fundus photographs. In CRVO, vein occlusion causes hypoxia, which is measured directly by retinal oximetry to confirm the diagnosis and measure severity. In both diseases, the change in oxygen levels is a consequence of disturbed blood flow with resulting tissue hypoxia and vascular endothelial growth factor (VEGF) production. In atrophic diseases, such as retinitis pigmentosa and glaucoma, retinal oxygen consumption is reduced and this is detected by retinal oximetry. Retinal oximetry correlates with visual field damage and retinal atrophy. It is an objective metabolic measure of the degree of retinal atrophy. Finally, the retina is part of the central nervous system tissue and reflects central nervous system diseases. In Alzheimer's disease, a change in retinal oxygen metabolism has been discovered.

CONCLUSIONS. Retinal oximetry is a novel, noninvasive technology that opens the field of metabolic imaging of the retina. Biomarkers in metabolic, ischemic, and atrophic diseases of the retina and central nervous system have been discovered.

Keywords: retina, oxygen, retinal oximetry, diabetic retinopathy, retinal vein occlusion, glaucoma, retinitis pigmentosa, Alzheimer's disease, brain, imaging, biomarker, pathophysiology

Retinal oximetry involves noninvasive spectrophotometric imaging of retinal blood vessels, which are part of central nervous system vasculature. In the decade since retinal oximetry has become readily available to clinical researchers, it has led to discovery of new biomarkers in several retinal diseases such as diabetic retinopathy, central retinal vein occlusion (CRVO), retinitis pigmentosa, and glaucoma, as well as diseases of the brain, including Alzheimer's disease. Further validation is needed in order to establish the utility of retinal oximetry biomarkers in clinical practice and trials.

TECHNOLOGY

The most common form of retinal oximetry uses conventional fundus cameras to image retinal vasculature (Fig. 1). The

acquisition of images is quick and safe and easily performed by anyone versed in fundus photography. It is easy for the patient and the only inconvenience is pupil dilation and the light flash, which is less intense than in conventional fundus photography (Fig. 1).^{1,2}

The technology has been described in detail.³ It typically involves a conventional fundus camera (Fig. 1) with specialized optics and camera(s) to capture images at two wavelengths simultaneously. Spectral analysis at two wavelengths measures the ratio of oxy- and deoxyhemoglobin in retinal arterioles and venules (optical density ratio, ODR). The percentage of hemoglobin oxygen saturation is approximately linear to ODR and can be measured in retinal arterioles and venules. Arteriovenous difference is calculated as the difference in oxygen saturation between arterioles and venules. Two companies have developed retinal oximeters, which are



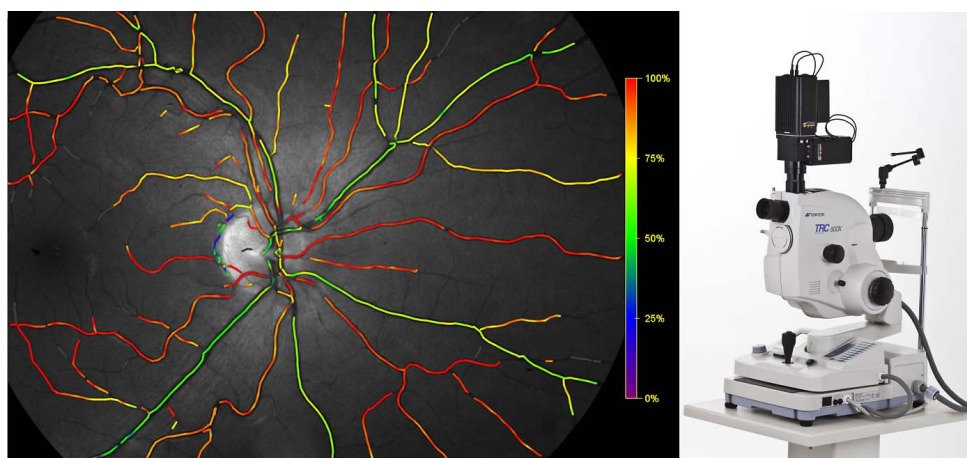


FIGURE 1. *Left:* Retinal oximetry image of a normal fundus. Color scale is on *right*. Arterioles are *red*, indicating 90% to 100% saturation, and venules are *green*, indicating saturation around 60%. *Right:* Oxymap T1 oximeter (Oxymap ehf. Reykjavik, Iceland), which is built on a conventional fundus camera.

commercially available: Oxymap in Reykjavik, Iceland, and Imedos in Jena, Germany. The Oxymap technology is already semiautomatic, and a fully automatic version for image analysis is forthcoming soon. Several research groups have developed retinal oximeters, which are used in their respective centers.

Retinal oximetry is remarkably stable. This reflects a robust technology and the stability of oxygen and other biochemical levels in the central nervous system. Test-retest trials show that the standard deviation in repeated measurements in the same individual is approximately 1%.⁴ Palsson et al.⁴ found low variability with mean and standard deviation of saturation measurements of $93.1\% \pm 2.3\%$ in arterioles and $64.9\% \pm 3.3\%$ in venules in a young adult cohort. Geirsdottir et al.² reported oxygen saturation to be $92.2\% \pm 3.7\%$ in retinal arterioles and $55.6\% \pm 6.3\%$ in venules in a large cohort of all ages. The low variability and high reproducibility of oximetry measurement is found not only in normal subjects but also in diseased retinas.⁵ The variability in normal cohorts is several times less than that seen with common clinical measurements such as intraocular pressure and optical coherence tomography measurements of the retina.

Retinal oximetry relies on visible light and can therefore be affected by optical media opacities. Oximetry studies on patients with cataract⁶ (Hardarson SH, et al. *IOVS* 2015;56:ARVO E-Abstract 3316) and tests with simulated cataracts^{7,8} have shown that image quality has to be taken into account when comparisons of oximetry values are made. It is possible to measure image quality in the Oxymap Analyzer Software, and this helps in detecting and controlling for possible biases in oximetry studies (Hardarson SH, et al. *IOVS* 2015;56:ARVO E-Abstract 3316).

DIABETIC RETINOPATHY

Retinal oxygen levels change with severity of diabetic retinopathy. This agrees with the ischemia-capillary non-perfusion that has long been known as a hallmark of the disease and associated with severity. Several reports show that venous retinal oxygen saturation is elevated in diabetic retinopathy (Figs. 2, 3).⁹⁻¹¹ The increase in venous saturation appears to be related to severity of retinopathy,^{10,11} and in patients with severe diabetic retinopathy, the oxygen saturation correlates with the severity of retinal ischemia.¹² Smaller arteriovenous difference in oxygen saturation (Figs. 2, 3)

reflects reduced oxygen delivery to tissue, which varies between the macular area and the retinal periphery.¹³ This is a consequence of maldistribution of blood flow due to capillary nonperfusion. The correlation between oxygen saturation and severity of retinopathy shows that retinal oxygen saturation measurement may serve as an objective biomarker for the severity of retinopathy (Figs. 2, 3).

Retinal oximetry measurements are continuous and linear and therefore much more precise than the conventional classification of fundus photographs, which we rely on today for grading retinopathy. Prospective studies are under way to further validate the oximetry biomarker in diabetic retinopathy.

Analysis of oximetry data in diabetic retinopathy suggests that retinal oximetry in diabetic patients can accurately identify eyes without retinopathy as well as eyes with retinopathy, even though a “gray zone” lies in between with eyes that cannot reliably be placed in either group (Fig. 4). Larger studies are under way and will further validate the correlation between oximetry measurements and conventional fundus photograph classification in diabetic retinopathy and establish the use of this biomarker in determining the presence, severity, and progression of diabetic retinopathy.

EFFECT OF LASER AND VITRECTOMY

Laser treatment and vitrectomy are both therapeutic for diabetic retinopathy. Both influence retinal oxygen metabolism, and this effect can be detected by retinal oximetry. Retinal photocoagulation destroys photoreceptors and adjacent tissue and reduces oxygen consumption of retina.¹⁴⁻¹⁶ This reduces hypoxia and vascular endothelial growth factor (VEGF) production. Retinal oximetry detects the effect of retinal laser treatment. Torp et al. (*IOVS* 2016;57:ARVO E-Abstract 6356) suggested that retinal venous oxygen saturation may be altered by panretinal photocoagulation. Jorgensen and Bek¹⁷ measured a slight increase in venous saturation in patients with proliferative retinopathy. The arteriovenous difference in saturation was, however, unchanged by both macular laser and panretinal photocoagulation. The diameter of the retinal vessels decreased for both groups, and if this is combined with unchanged arteriovenous difference in saturation, it suggests that less oxygen is extracted from the retinal vasculature after laser treatment.

Vitrectomy also improves retinal oxygenation and reduces hypoxia. This has been demonstrated in experimental ani-

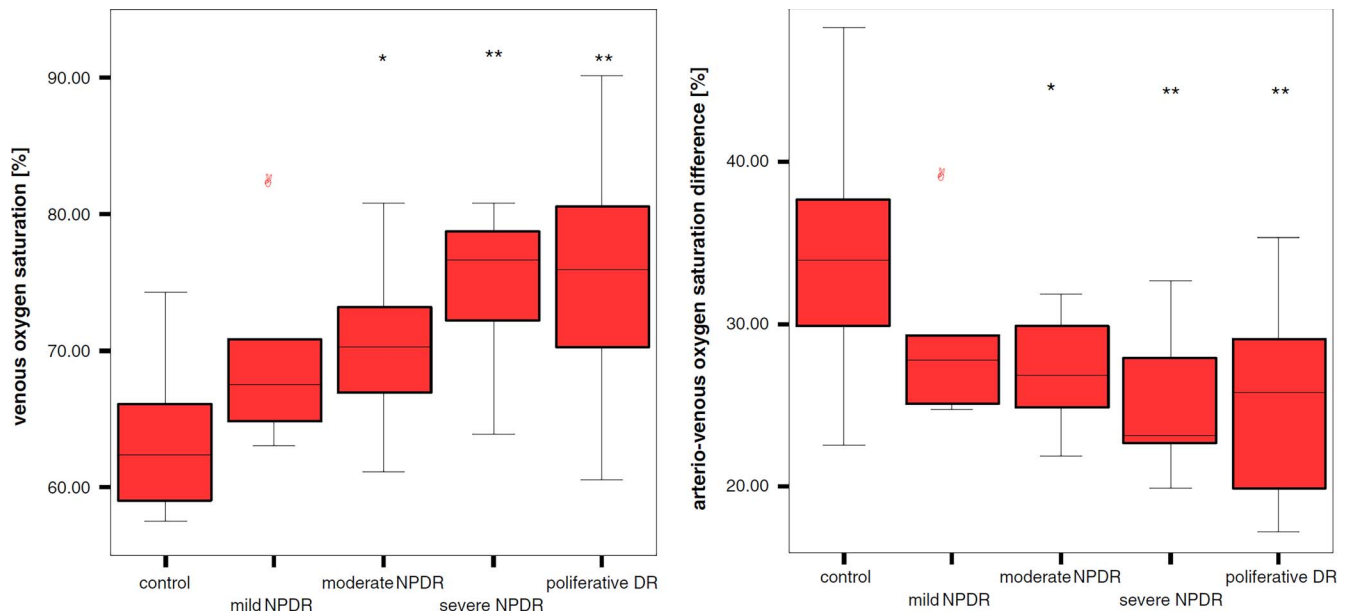


FIGURE 2. Retinal oxygen saturation in patients with diabetes and normal controls.¹⁰ The graph on the left shows retinal venous oxygen saturation, and the graph to the right shows arteriovenous difference. NPDR, nonproliferative diabetic retinopathy. DR, diabetic retinopathy. Published with permission from Hammer M, Vilser W, Riemer T, et al. Diabetic patients with retinopathy show increased retinal venous oxygen saturation. *Graefes Arch Clin Exp Ophthalmol*. 2009;247:1025–1030. © Springer-Verlag 2009.

mals^{14,16,18} and human patients.¹⁹ Three reports have been published on retinal oximetry before and after vitrectomy, and all have concluded that oxygenation is improved. Lim et al.²⁰ found that both arterial and venous oxygen saturation increased after vitrectomy, although the interpretation of their results is complicated due to the fact that phacoemulsification was performed at the same time. Sin et al.²¹ measured patients with macular hole or epiretinal membrane and found that

retinal venous oxygen saturation increased following vitrectomy while arterial saturation was unchanged. In a later study, Sin et al.²² found that venous saturation increased in nondiabetic patients and this was maintained one year after the surgery.

There is good correlation between findings with invasive oxygen probes in animals and humans and retinal oximetry findings. Both show treatment effect in patients following retinal laser treatment and vitrectomy.

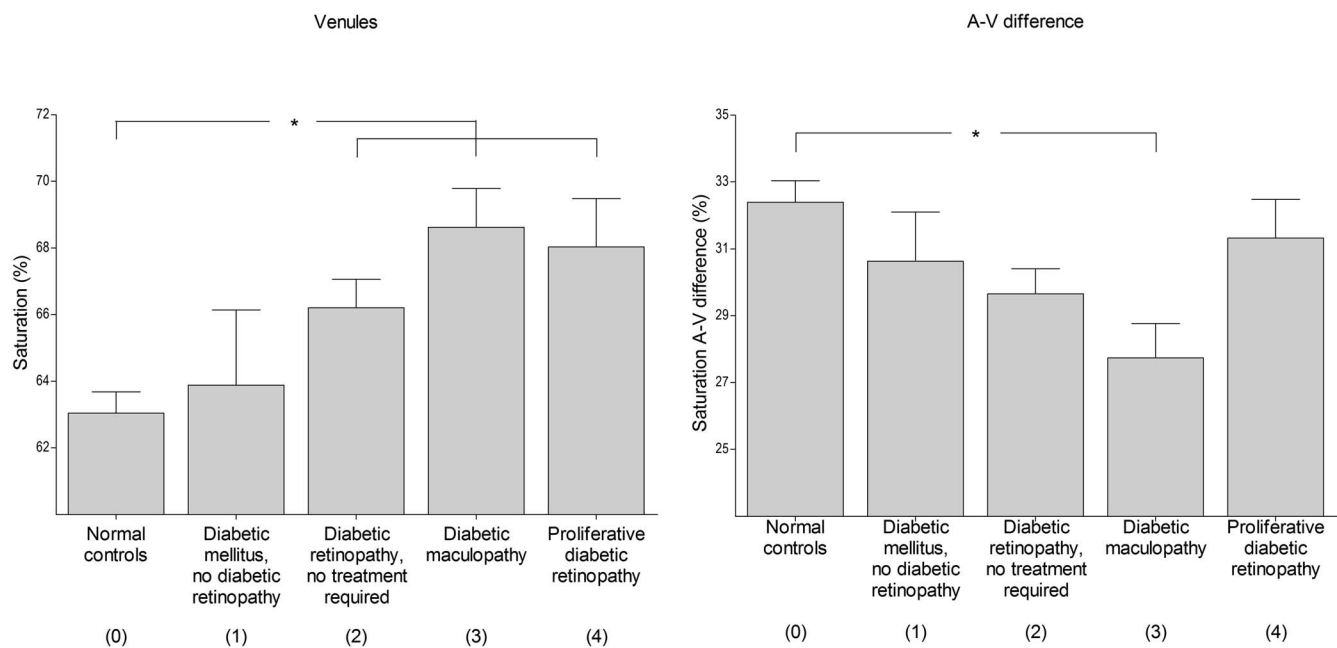


FIGURE 3. Retinal oxygen saturation in patients with diabetes and normal controls.¹¹ The graph on the left shows retinal venous oxygen saturation, and the graph to the right shows arteriovenous difference. Published with permission from Jørgensen CM, Hardarson SH, Bek T. The oxygen saturation in retinal vessels from diabetic patients depends on the severity and type of vision-threatening retinopathy. *Acta Ophthalmol*. 2014;92:34–39. © 2013 Acta Ophthalmologica Scandinavica Foundation. Published by John Wiley & Sons Ltd.

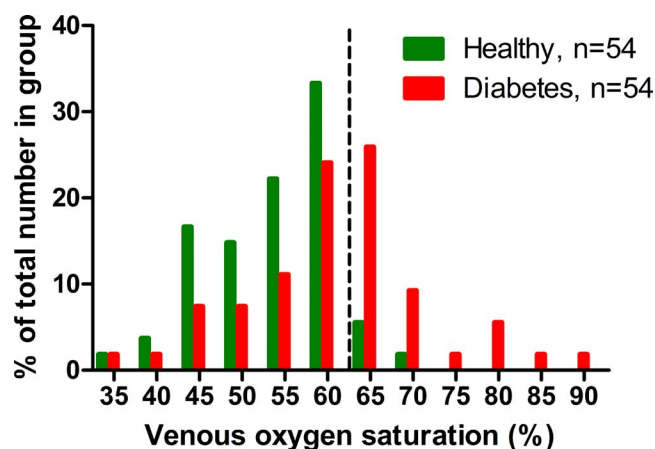


FIGURE 4. Distribution of venous oxygen saturation in healthy subjects (green) and diabetic patients (red). Five percent of saturation values were above 63% in the healthy cohort (dotted line). Venous saturation in diabetic patients was above 63% in 46% of the patients (25 of 54 patients). The ratio of diabetic patients with venous saturation higher than 63% increased with severity of retinopathy: 25% of diabetic patients without retinopathy (4/16 patients) had venous saturation above 63%; 46% of patients with nonproliferative retinopathy (11/24) were above the 63% line; and 71% of patients with PDR and history of treatment (10/14).

ANTI-VEGF TREATMENT

The advent of anti-VEGF treatment has improved the visual prognosis for patients with diabetic retinopathy considerably. The treatment can reduce neovascularization in proliferative diabetic retinopathy, but can also increase visual acuity and reduce macular edema in diabetic maculopathy. However, the effect of the treatment is individually varying, and there is a need for biomarkers to differentiate patients who will benefit from treatment from those who will not. Interestingly, a recent study has shown that the oxygen saturation in retinal arterioles together with the arterial blood pressure contributes significantly to predicting visual acuity and central retinal thickness after anti-VEGF treatment of diabetic maculopathy.¹³ This suggests that the retinal oxygen saturation together with other

risk factors comprises biomarkers that could be implemented into risk models for predicting the effect of anti-VEGF treatment of diabetic maculopathy.

CENTRAL RETINAL VEIN OCCLUSION

CRVO is characterized by venous occlusion, impaired blood flow, tissue hypoxia and consequent retinal edema, reduced function, and iris neovascularization. Retinal hypoxia has been confirmed with intravitreal oxygen probes.²³

Retinal oximetry measures hypoxia in retinal venules, which is variable between patients and may be very severe^{24–26} (Fig. 5). A significant difference is seen between healthy fellow eyes and eyes with CRVO. Measurement of oxygen levels may be more precise than assessment of ischemia on fluorescein angiograms or evaluation of fundus photographs, and distinguishes between healthy and CRVO eyes (Fig. 6).

The paper by Traustason et al.²⁶ shows that the oxygen saturation in the retinal veins has a higher variance than in the arterioles. This might reflect aspects of pathophysiology with predictive value, and thereby be a potential biomarker for the severity of metabolic dysregulation in the retinal area affected by the occlusion. Additionally, a recent study has shown that visual acuity correlates negatively with the oxygen saturation in retinal arterioles and positively with the saturation in retinal venules in patients with CRVO.²⁷ However, the retinal oxygen saturation does not predict the visual outcome in CRVO patients three months after three monthly injections with anti-VEGF medication. Therefore, retinal oxygen saturation may help in understanding hemodynamic changes in the retinal circulation during the acute stages of the disease, but is probably less suited as a biomarker for long-term visual outcome in the disease.

PHYSIOLOGY OF ISCHEMIC RETINOPATHIES AND RETINAL OXIMETRY

The pathophysiological axis of the ischemic retinopathies involves ischemia-hypoxia-VEGF production edema/neovascularization (Fig. 7) in addition to inflammatory cytokines and

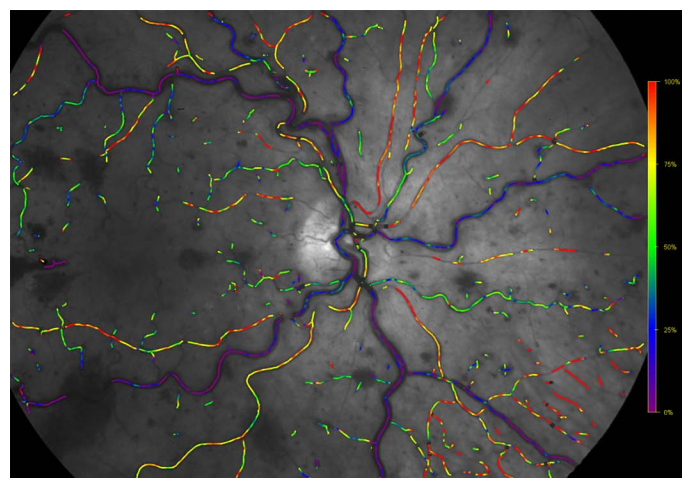
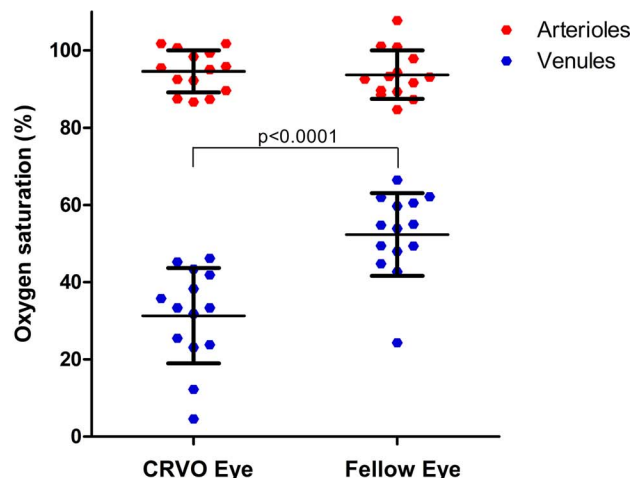


FIGURE 5. Retinal oximetry image of an eye with central retinal vein occlusion, CRVO. Compare with normal fundus oximetry in Figure 1. The blue color of the venules indicates severe hypoxemia, in the range of 20% saturation. The graph on the right shows oxygen saturation measurements for retinal venules (blue) and arterioles (red).²⁴ Significant hypoxia is seen in retinal venules in CRVO eyes compared to healthy fellow eyes. Published with permission from Eliasdottir TS, Bragason D, Hardarson SH, Kristjansdottir G, Stefánsson E. Venous oxygen saturation is reduced and variable in central retinal vein occlusion. *Graefes Arch Clin Exp Ophthalmol.* 2015;253:1653–661. © Springer-Verlag Berlin Heidelberg 2014.



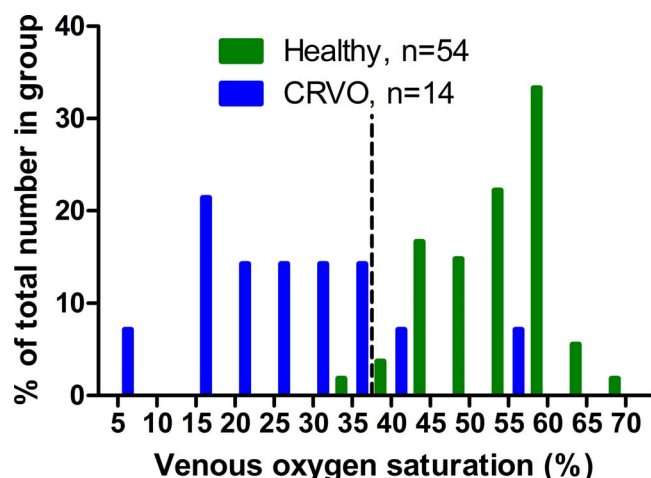


FIGURE 6. Distribution of venous oxygen saturation in healthy eyes (green) and eyes with CRVO (blue). Five percent of venous saturation values in healthy eyes were below 38% (dotted line). Eleven out of 14 CRVO patients measured (79%) had venous saturation lower than 38%.

other factors. Hypoxia is central in this pathophysiology and the main stimulant of VEGF production, which is the main target of treatment and agent of edema formation and new vessel growth. Oximetry addresses the central component of pathophysiology of the ischemic retinopathies. Structural changes seen on fundus photographs involve consequences of the pathophysiological process, which take place later in the process.

RETINITIS PIGMENTOSA

Eysteinnsson et al.²⁸ demonstrated that saturation of retinal veins is elevated in retinitis pigmentosa. Todorova et al.³¹ and other groups reported that the oximetry and retinal vessel attenuation changes correlate well with retinal atrophy and retinal function deterioration as seen by retinal thickness measurements by optical coherence tomography and electrophysiological assessment.^{29–32}

The change in retinal oxygen saturation in retinitis pigmentosa is clearly a consequence of the cell death and reduced oxygen consumption. Oximetry measures the cell loss and thereby the severity of disease. It may offer an objective and quantitative measure of the progression of atrophy in retinitis pigmentosa and presumably in other atrophic retinal diseases. Oximetry can distinguish between eyes with advanced retinitis pigmentosa and healthy eyes. Oximetry can also distinguish retinitis pigmentosa patients from other patients with inherited retinal disease.^{32,33} All studies to date have been cross-sectional, and prospective studies are needed to fully validate the clinical use of oximetry.

GLAUCOMA

Retinal oximetry measures the reduced oxygen extraction that is a consequence of atrophy in glaucoma. In cross-sectional studies, the saturation of the retinal venules is elevated in accordance with worse visual field scores, thinner nerve fiber layer thickness, and reduced optic disc rim area (Fig. 8). In other words, with more advanced glaucomatous atrophy, the venous saturation rises and the arteriovenous difference is reduced.^{34,35} The causal relationship is likely reduced oxygen consumption caused by cell death and consequently reduced

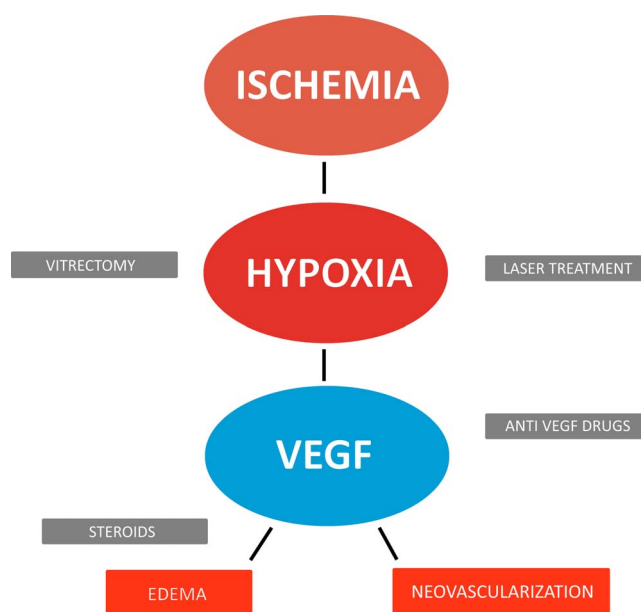


FIGURE 7. The flow diagram describes the central position of hypoxia in the pathophysiological process. Hypoxia is the consequence of ischemia and stimulates VEGF formation. Laser photocoagulation reduces retinal hypoxia as does vitrectomy. VEGF (vascular endothelial growth factor) levels are reduced by anti-VEGF drugs, steroids, and also vitrectomy. VEGF induces retinal edema and new vessel formation.

oxygen delivery. Prospective studies remain to be done to further validate this biomarker as a measure of severity and progression of glaucomatous damage.

ALZHEIMER'S DISEASE AND MULTIPLE SCLEROSIS

The retina and brain are parts of the central nervous system. The accessibility of the retina for imaging creates an interest in looking for structural and metabolic changes that may reflect similar abnormalities in the brain. Optical coherence tomography studies have shown thinning of nerve fiber layer and other structural anomalies in the retina in brain diseases such as Alzheimer's disease, multiple sclerosis, and Parkinson's disease.

Retinal oximetry offers an opportunity to add metabolic imaging in the belief that metabolic changes in brain disease may be reflected in the retina. Einarsson et al.³⁷ were the first to show metabolic changes in retina in brain disease, when they reported oximetry abnormalities in retinas of Alzheimer's patients compared with a healthy cohort. These findings have recently been confirmed and extended to patients with mild cognitive impairment (Traustadottir VD, et al. *IOVS* 2017;58:ARVO E-Abstract 3103).

Also in multiple sclerosis there are alterations in retinal oximetry findings. Saturation in retinal venules is higher in eyes with multiple sclerosis than in healthy controls (Olafsdottir OB, et al. *IOVS* 2017;58:ARVO E-Abstract 3104).

Of interest, retinal oxygen saturation has been found to be affected in cases with giant cell arteritis without ocular symptoms. This could confirm a subclinical presentation of central nervous inflammatory occlusive vasculitis.³⁸

CONCLUSIONS

Most retinal diseases have an ischemic and/or atrophic component, which directly affects oxygen metabolism. It is

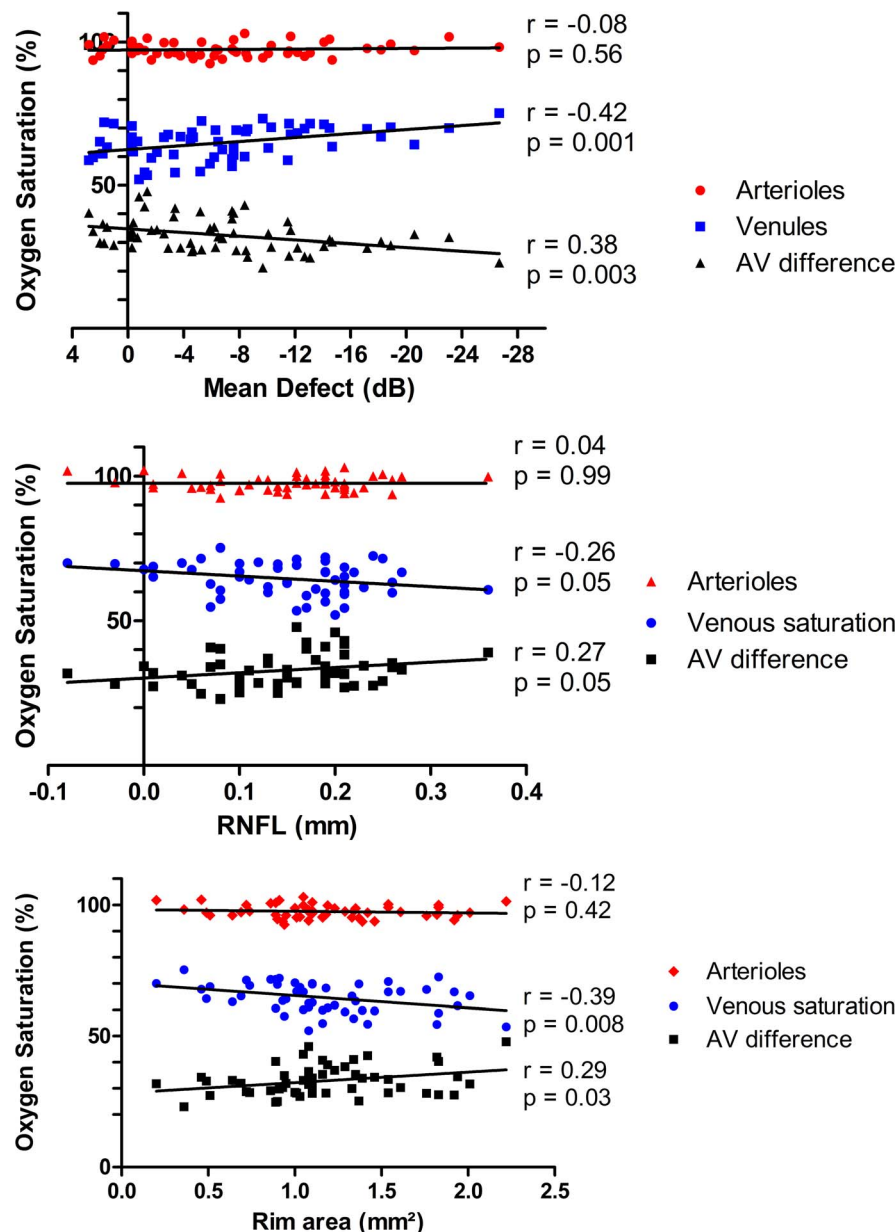


FIGURE 8. Retinal oxygen saturation is correlated with glaucomatous atrophy. Retinal venous saturation (blue) rises with worsening visual field (top), thinner nerve fiber layer (RNFL), and reduced optic disc rim area (bottom). Arteriovenous difference (black) decreases with worsening visual field, thinner nerve fiber layer, and reduced optic disc rim area. Note that visual field worsens toward the right of the image, whereas retinal nerve fiber thinning and decreased optic nerve rim area go toward the left of the images.^{35,36} Published with permission from Vandewalle E, Abegão Pinto L, Olafsdottir OB, et al. Oximetry in glaucoma: correlation of metabolic change with structural and functional damage. *Acta Ophthalmol.* 2014;92:105–110. © 2013 The Authors. *Acta Ophthalmologica* © 2013 Acta Ophthalmologica Scandinavica Foundation.

not surprising that retinal oximetry is sensitive to pathophysiological changes in many of these diseases. The ischemic retinopathies, such as diabetic retinopathy and CRVO, involve impaired oxygen delivery to tissue and hypoxia, which is measured by retinal oximetry. In the atrophic diseases such as retinitis pigmentosa and glaucoma, it is atrophy and reduced oxygen consumption that affect oximetry measurements. In both ischemic and atrophic disease there is a correlation between oximetry readings and the severity of disease. This suggests that retinal oximetry may serve as an objective biomarker for the presence and severity of ischemic and atrophic retinal diseases.

The potential for oximetry as a biomarker for diagnosis and treatment of retinal disease has not yet been fully explored. There is a need to extend the number of prospective studies investigating the predictive value of retinal oxygen saturation for the prognosis of ischemic and atrophic retinal diseases.

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