
OXIMETRY: RECENT INSIGHTS INTO RETINAL VASOPATHIES AND GLAUCOMA

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ABSTRACT

This review will highlight a new technology and recent insights into measuring retinal oxygen saturation in several ophthalmic diseases. A growing body of evidence suggests that disturbances in retinal blood flow and oxygenation are related to several retinopathies and glaucoma, which can severely impair vision. The retinal oximeter may allow researchers and physicians to gain deeper insights into retinal physiology and clarify the impact of ischemia on retinal health and function. There are two commercially available systems to measure retinal oxygen saturation: the Oxymap retinal oximeter (Reykjavik, Iceland) and the Imedos Systems UG (Jena, Germany). In this review we will focus on the results obtained with Oxymap.

Direct and non-invasive measurement of retinal oxygen saturation have potentially useful diagnostic and therapeutic indications in various eye diseases such as diabetic retinopathy, age-related macular degeneration, central retinal vein and artery occlusion, anterior ischemic optic neuropathy and retinopathy of prematurity.

Despite several limitations, oxygen saturation assessment in the retinal vessels is a significant advancement in the understanding of ocular diseases. Nevertheless, further studies are needed to validate the use of oximetry in retinal vasopathies and glaucoma.

KEYWORDS

Ocular circulation, Oximetry, Oxygen saturation, Retinal vasopathies, Glaucomatous optic neuropathy

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Submitted: Jan 02, 2012

Accepted: Jan 25, 2012

Vascular pathologies play an important role in the pathogenesis and the progression of a number of ophthalmic diseases. The assessment of ocular hemodynamics is potentially useful in the early detection and the differentiation of abnormalities. Ocular blood flow and oxygenation are crucial in ophthalmic circulatory investigation (1). Recently, a non-invasive technique has been developed to measure retinal oxygen saturation.

OCULAR HEMODYNAMICS

OCULAR CIRCULATION

The ocular circulation is complex because of the necessity to supply different ocular structures with nutrients without interfering with the visual pathways (2).

Ocular blood flow (OBF) is determined by ocular perfusion pressure and vascular tone. Ocular perfusion pressure is defined as an arterio-venous pressure difference, meaning a net pressure gradient causing blood flow into the eye (3). OBF can be expressed by the Hagen-Poiseuille law, which states that flow is equal to the perfusion pressure divided by the resistance to flow. Since the retinal venous pressure is equal to, or at least positively correlated with the intraocular pressure (IOP), it can be calculated as $OBF = (OAP - IOP) / R$ where OAP is the ophthalmic artery pressure and R is the resistance to flow (4).

The retinal circulation is characterized by a low level of flow and a high level of oxygen extraction and is strictly regulated to maintain an adequate oxygen supply (2,5). The choroidal circulation is characterized by very high flow which accounts for 85% of the total blood flow in the eye, and a low oxygen extraction. Retinal vessels are supplied by the central retinal artery, which is a branch of the ophthalmic artery (2). Blood supply to the optic nerve head is unique. The superficial layer of the optic nerve head receives its blood supply via small branches from the central retinal artery. The prelaminar region, a small area anterior to the lamina cribrosa, is mainly supplied by branches from the recurrent choroid arterioles and the short posterior ciliary arteries. Venous drainage of the op-

tic nerve head occurs through the central retinal vein (2,6). The oxygen tension of the optic nerve (PO_2) is regulated by three parameters: the perfusion pressure, the resistance in the blood vessels and the oxygen consumption of the tissues (7,8).

AUTOREGULATION

Ocular blood flow is highly regulated in order to adapt to altering metabolic needs caused by varying visual function, to compensate for changes in perfusion pressure and finally to maintain a stable temperature at the back of the eye (2,3,9).

Retinal oxygen tone is tightly controlled by autoregulation of the vessel diameter (vasoconstriction or vasodilatation), meaning that within a certain range, flow is independent of ocular perfusion pressure (2,3,7,10). When the intraocular pressure is increased, the arterioles dilate and decrease their resistance to meet the decreased perfusion pressure of the eye. However, if the IOP is increased above 40 mmHg or the ocular perfusion pressure decreased below 50 mmHg the autoregulation is overwhelmed and the optic nerve becomes hypoxic. This fall in PO_2 is in a linear fashion with the increased IOP (7). Any imbalance of the autoregulation may result in a disturbance of the microcirculation (10).

IMAGING TECHNIQUES

Ocular hemodynamic evaluation requires the use of several imaging modalities.

OCULAR BLOOD FLOW – Different technologies for measuring ocular blood flow have been developed. Among them, the vessel caliber assessment by fundus photography, the scanning laser ophthalmoscopic angiography with fluorescein and indocyanine green, the laser doppler flowmetry, the ocular pulse measurement and the colour doppler imaging (1,8). However, it should be noted that comparing results from similar studies employing different assessment techniques is difficult since each technique evaluates a particular aspect of OBF (1,3,8,11,12). Moreover, no single imaging device up to date is capable of evaluating the ocular circulation in all of its relevant ocular tissue beds (1).

OCULAR OXYGENATION – The oxygen utilization reflecting the metabolic status of a distinctive area of the retina can be calculated from the diameter of the supplying artery and vein, the hemoglobin oxygenation and the velocity of the blood (13). A non-invasive retinal oximeter has been developed which allows to assess relative retinal oxygen saturation levels (satO_2) and retinal vessel width. This technology provides information on the impact of ischemia on retinal health and function (1,4,11,14-17). An important advantage of this technique is that the measurement area is large and little expertise is needed to acquire a pseudocolour fundus image of retinal vessel oxygenation. Presently, the retinal oximeter is only used for clinical research purposes, and is not intended yet to aid in diagnosing or monitoring ophthalmic diseases (14).

OXIMETRY

THE OXYMAP RETINAL OXIMETER

The Oxymap retinal oximeter is a spectrophotometric device based on a fundus camera which is attached to a beam splitter and a digital camera (*Figure 1*). It simultaneously captures images of the retina at two wavelengths: one is sensitive to changes in the percentage of oxygen bound to hemoglobin (605 nm) and the second is an isobestic wavelength meaning that light absorbance is similar for oxygenated and deoxygenated hemoglobin (586 nm) (4,5,7,11,15,18,19).

The fundus view shows colour-coded oxygen saturation values on top of a grayscale retinal image. In healthy eyes, the arterioles are close to 90-100% satO_2 and are coloured in “warm” colours (red to orange) whereas the venules are closer to 50-60% satO_2 and are coloured in “cold” colours (green to blue) (18). Specialized software automatically selects measurement points on the oximetry images and calculates the optical density (OD, absorbance) of retinal vessels at both wavelengths, as the logarithm of the ratio of light intensities inside the vessels versus the outside background. The ratio of the two optical densities is approximately linearly related to hemoglobin oxygen saturation, since the oxygen saturation is equal to



Fig. 1: The Oxymap retinal oximeter. ©Oxymap ehf.

the percentage of oxygenated hemoglobin within total hemoglobin (1,6,7,15-17). Numerical or graphical information of selected vessel segments such as satO_2 and vessel width are shown (14). Furthermore, it calculates the difference between the oxygen delivered to and away from the retina (the arteriovenous difference) (11). For this purpose, the method is based on the relationship between light transmittance and oxygen saturation. According to Lambert and Beer, light transmission through a solution diminishes logarithmically as the concentration of the solution and the distance through it increases (11). Oxygenated and deoxygenated hemoglobin have different light absorption spectra. By analyzing the light absorbance of blood at these two wavelengths, the oxygenation of hemoglobin can be estimated. Moreover, Oxymap is sensitive to changes in oxygen saturation. This sensitivity is essential to be of value for measuring changes associated with disease or treatment (14,17).

OXIMETRY AND RETINAL VASOPATHIES

Hypoxia plays a role in the pathophysiology of several retinal vasopathies (14,20).

1. Diabetic retinopathy

Diabetic retinopathy (DR) has been linked to disturbances in the vascular system. Tissue hypoxia plays an important role in the progression of DR. Longstanding diabetes mellitus may lead to an imbalanced autoregulation and a disturbance of the microcirculation, resulting in occlusions and obliterations in the capillary bed and a formation of arteriovenous shunt vessels. These structural changes are typical for diabetic microangiopathy (10,20,21). Retinal oximetry can be used to investigate the effect of the disturbed microcirculation on retinal vessel oxygen saturation.

A study by Hammer et al. (2009) found an increase in the venous hemoglobin oxygenation with the progression of DR up to the stage of severe non-proliferative DR while no further venous hemoglobin oxygenation increase was observed. Still, an enhanced venous saturation means a reduced oxygen release to the tissue in the capillary bed resulting in tissue hypoxia. The structural changes in diabetic microangiopathy are presumably responsible for this decreased oxygen delivery, which is critical for the maintenance of retinal structures and function. *Figure 2* shows saturation maps of a

healthy subject (right) and a patient suffering from DR (left). In the healthy subject, blue colour of branch venules indicate a satO_2 of about 50%, whereas venules, supplying the macula, reveal a satO_2 clearly higher than 60%. In DR, all venules show an increased satO_2 , indicated by the green to orange pseudocolour (10). A recent study by Hardarson et al. (2011) confirmed that retinal vessel oxygen saturation is higher in all categories of DR compared with healthy subjects (22). Thus the investigation of oxygen supply may be indicative as a diagnostic marker as well as for therapy monitoring in DR.

2. Age-related macular degeneration

There are several theories of pathogenesis of age-related macular degeneration (AMD), including primary retinal pigment epithelium (RPE) senescence, primary ocular perfusion abnormalities and genetic defects. The RPE metabolically supports and maintains the photoreceptors. However, senescence cannot fully explain the wide variety of clinical presentations. Another pathogenic theory involves primary vascular changes in the choroid leading to disturbed oxygenation which secondarily affects the RPE. Cardiovascular risk factors, such as hypertension, tobacco use and high fat diets, are risk factors for AMD that suggest a vascular pathogenesis (8).

A study by Grunwald et al. (2005) showed a correlation between the decrease in choroidal circulatory parameters and the severity of AMD, pointing towards a potential role for ischemia (23,24). Oximetry can play an important role in further understanding of these disease processes. Until now, there is no literature regarding the role of oximetry in AMD.

3. Retinal vein occlusion

Central retinal vein occlusion (CRVO) disturbs retinal blood circulation. On fluorescein angiography, it is associated with a variable

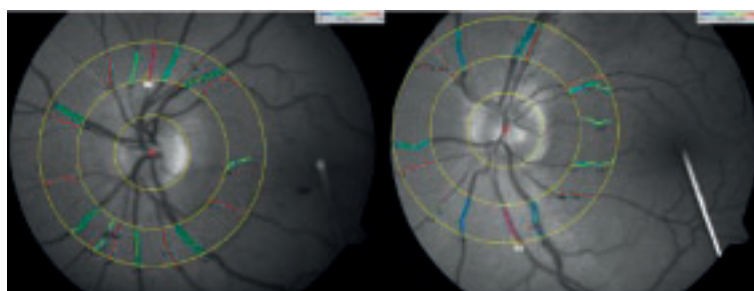


Fig. 2: Pseudocolour representation of retinal vessel hemoglobin oxygenation. Left: patient suffering from moderate non-proliferative diabetic retinopathy. Right: healthy control subject (10).

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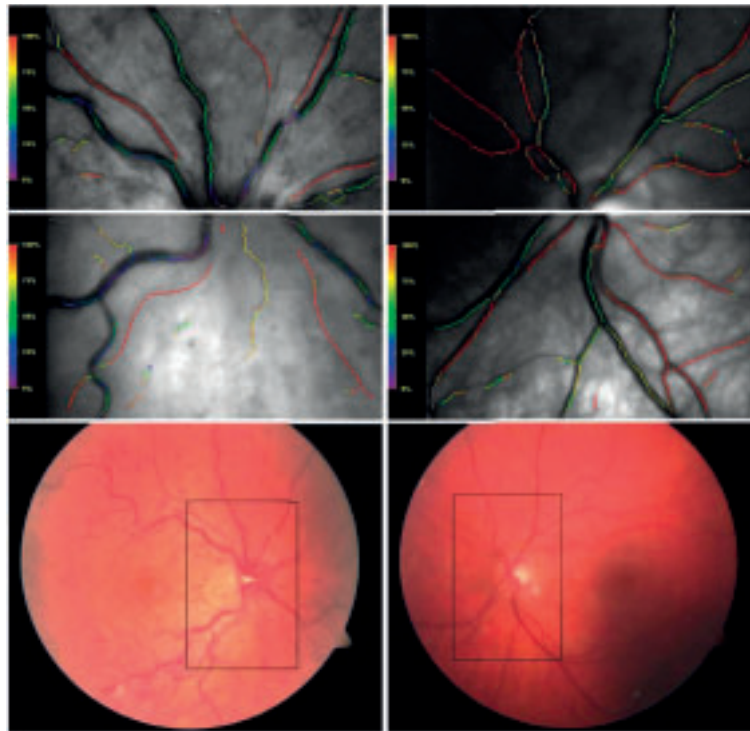


Fig. 3: Oxygen saturation map. Left: eye affected by CRVO. Right: healthy control subject (15). Reprinted from *American Journal of Ophthalmology*, 150, Hardarson SH, Stefánsson E, Oxygen saturation in central retinal vein occlusion, 871-5, 2010, with permission from Elsevier.

degree of capillary nonperfusion. CRVO can therefore be expected to cause retinal hypoxia and can be measured with the retinal oximeter. The retinal hypoxia constitutes a reliable measure of the severity of occlusion. Hypoxic inductions of cytokines, for example the vascular endothelial growth factor (VEGF), play a central role in the consequences of CRVO such as retinal edema and iris neovascularisation.

A study by Hardarson et al. (2010) found that oxygen saturation in retinal venules is lower in eyes with CRVO compared to healthy eyes, whereas the arteriolar saturation is unaffected (Figure 3). The most likely reason for the lower venular oxygen saturation is the decreased retinal blood flow which is attributable to the occlusion (15). Another study by Hardarson et al. (2011) showed that venular saturation is highly variable between patients in both central and branch retinal vein occlusion. This may reflect variable severity of disease, degree of oc-

clusion, recanalization, collateral circulation, tissue atrophy, arteriovenous diffusion or vitreal transport of oxygen (25).

4. Retinal artery occlusion

Central retinal artery occlusion (CRAO) has a pathomechanism that includes embolism, vasoobliteration and vascular compression (20). A case series from Stefánsson et al. (based on a poster "Retinal oxygenation in patients with central retinal artery occlusion", ARVO 2009) found that retinal vessel oxygen saturation in patients with CRAO is initially decreased but may reach normal values after restoration of blood flow. Cell death, indicated by permanent vision loss, decreases oxygen consumption and influences the saturation values. A study by Gehlert et al. (2010) has confirmed these results. The retinal hemoglobin oxygenation in patients with branch retinal artery occlusion has been measured before and after a rheological and in-

traocular pressure reduction therapy. An increase of the arterial haemoglobin oxygenation was observed after this therapy (26).

5. Anterior ischemic optic neuropathy

Non-arteritic anterior ischemic optic neuropathy (AION) is the result of a partial or total infarction of the optic nerve head caused by occlusion of the short posterior ciliary arteries. Arteritic AION, on the other hand, is caused by giant cell arteritis (20). Both pathologies are characterized by vascular changes in the fundus, and further knowledge about oxygen saturation would be useful. At present, there is no literature about the role of oximetry in AION.

6. Retinopathy of prematurity

The pathophysiology of retinopathy of prematurity (ROP) has been known for decades. It develops in two main stages: relative hyperoxia, followed by a stage of hypoxia. A retinal oximeter would be helpful to measure oxygen saturation in retinal blood vessels. In the future, this non-invasively technique might be applied to the newborn to make sure that the therapy consisting in oxygen mixture in breathing air, illumination and retinal ablation is of the appropriate amount to give the desired oxygen saturation in the retina (27).

7. Glaucomatous optic neuropathy

The exact pathogenesis of glaucomatous optic neuropathy (GON) is still unknown (4). A mechanical and a vascular theory have been described. Apart from the mechanical effects of lowering IOP, the beneficial effects may also be due to better perfusion and oxygenation of the optic nerve, thereby improving the energy metabolism (7,14).

MECHANICAL THEORY – Increased IOP causes stretching of the laminar beams and damage to the retinal ganglion cell axons (2). Both a stable increase in IOP and IOP fluctuations have been identified as risk factors for glaucoma and its progression (6). A number of conditions such as congenital glaucoma, angle-closure glaucoma or secondary glaucoma clearly have illustrated that increased IOP is sufficient to lead

to GON. However, GON may develop at any level of IOP and only a minority of people with elevated IOP will progress to glaucoma (2,16,28).

VASCULAR THEORY – Evidence shows that ocular blood flow in glaucomatous eyes is reduced, or its regulation is disturbed compared to healthy eyes (12,14,29). However, it is still unknown whether the decreased OBF is involved in the etiology of glaucoma, or whether it is secondary to a loss of retinal ganglion cells and a decrease in the corresponding metabolic demand for oxygen and nutrients (3). The disruption of OBF is unlikely to be due to IOP alone, because it is found in all parts of the eye (iris, retina, choroid, optic nerve head) as well as retrolubar and even peripheral (2,6,9). Furthermore, in some patients OBF reduction precedes GON (2). The major cause is vascular dysregulation, leading to both low perfusion pressure and insufficient autoregulation (2,6,7,29,30). If the perfusion pressure of the eye is above 50 mmHg, the risk of optic nerve atrophy is low. This risk roughly doubles if the perfusion pressure is between 30 and 49 mmHg and increases more than 6-fold if the perfusion pressure falls below 30 mmHg (7,30). This instability of OBF may lead to ischemia and reperfusion damage (2,6). The role of hypoxia is supported by the increased staining of hypoxia-induced factor (HIF-1 α) in the retina and optic nerve of patients with glaucoma compared with healthy individuals (4). There is also evidence of an interrelationship between OBF and oxygen in the pathogenesis of GON. The metabolism of oxygen by cells can generate potentially deleterious reactive oxygen species. This oxidative stress may be a cause of increased IOP by triggering trabecular meshwork degeneration and thus contributing to alterations in the aqueous outflow pathway (9).

Patients with either primary open-angle glaucoma (POAG) or normal tension glaucoma (NTG) have various OBF deficits (2,8). A deficient regulation of ocular perfusion of the proximal portion of the optic nerve plays an important role in glaucomatous damage (2,7,10,31). POAG has been found to be associated with generalized vascular abnormalities leading to reduced blood flow including systemic hypertension, nocturnal or positional hypotension, atherosclerosis, optic disk haemorrhage, vasospasm seen

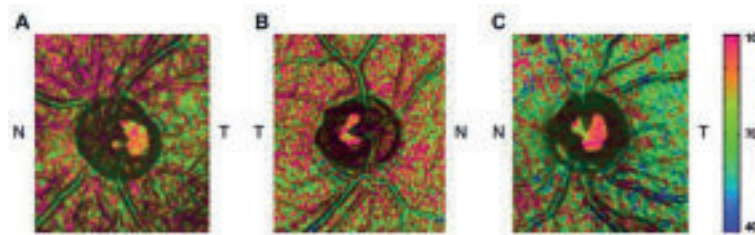


Fig. 4: Oxygen saturation map (T=temporal; N=nasal). A: Healthy subject - mainly red to yellow suggesting OS level to be more than 80%. B: High-tension glaucoma - less red dots, being greenish in colour. C: Low-tension glaucoma - dominantly green to blue dots, suggesting OS level between 70 and 80% (16).

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in migraine and Raynaud's disease and a defective vascular autoregulation (31-35). Sleep-associated diseases, like sleep apnea syndrome, might also be of interest (34). The factors known to cause atherosclerosis are also risk factors for an increase in IOP: age, smoking, dyslipidemia, diabetes mellitus, male sex and obesity (6). It is essential that these risk factors could be identified to improve diagnostic and therapeutic approaches (32).

OXIMETRY – Oxygen saturation measurement may be a novel tool for studying glaucoma patients. In a study by Michelson et al. (2006), oxygen saturation was measured in retinal arterioles and venules from both normal subjects and patients with open-angle glaucoma. The oxygen saturation in arterioles decreased significantly with increasing glaucomatous damage determined by the rim area. In contrast, oxygen saturation in retinal venules was unchanged compared with the control group (*Figure 4*) (16). There was also a negative correlation between the glaucomatous damage and the retinal arteriovenous saturation difference. This indicates an altered ratio between oxygen consumption and retinal oxygen supply in glaucomatous eyes, possibly related to tissue atrophy (32). However, this explanation is still hypothetical, since the relation between the oximetry results and structural changes in the optic nerve has not been studied yet.

DIFFICULTIES AND LIMITATIONS

The measurement of absolute values of oxygen saturation is still difficult. The two-dimen-

sional resolution is not accurate enough to measure the oxygen saturation level of a precise point like an area over the retinal vasculature. In addition, microsaccades and eye wandering cannot be avoided during the measurement due to bright light, even though an eye tracking device is used (16). Finally, the dual-wavelength method does not provide absolute oxygen saturation measurements (11).

CONCLUSION

This overview learned that despite several limitations, oxygen saturation assessment represents an exciting and promising advancement in the understanding of ocular diseases. However, data in the literature permitting precise conclusions are rare. Regarding retinal vasopathies only the few studies about oximetry in diabetic retinopathy and central retinal vein and artery occlusion, which were discussed in this review, showed some conclusive results. Moreover, the study of the oximetry in glaucoma is still in its preliminary phase. Hence, further studies will be needed to confirm and further expand the use of oximetry in ophthalmic diseases. Indeed, as with any newly emerging imaging device, additional improvements are required before true tissue oxygenation levels can be validated.

The authors acknowledge dr. M. Hammer for his critical reading of this review.

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