Retinal Oxygen Saturation Correlates With Visual Acuity but Does Not Predict Outcome After Anti-VEGF Treatment in Central Retinal Vein Occlusion

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Occlusion of the central retinal vein (CRVO) is a frequent cause of visual loss, but the advent of anti-VEGF treatment has improved the visual prognosis in CRVO considerably. The presence of retinal ischemia in CRVO worsens the visual prognosis, and the severity of this condition can be studied by fluorescein angiography, which allows a semiquantitative evaluation of areas of capillary nonperfusion. However, the examination is invasive and functional measures such as visual acuity, impaired afferent pupil response, and electroretinography have been shown to be superior than the degree of ischemia for predicting the visual prognosis in CRVO. Retinal ischemia leads to hypoxia in the larger retinal vessels, which can be measured quantitatively by oximetry based on fundus photographs obtained at two different wavelengths. Previous studies have confirmed that the oxygen saturation is reduced in the larger retinal venules in patients with CRVO, and that the oxygen saturation improves after treatment of the disease with anti-VEGF medication. However, the relation between visual acuity and retinal oxygen saturation and the predictive value of retinal oxygen saturation for visual outcome in patients with CRVO have not been studied in detail.

Therefore, retinal oximetry was performed in 91 patients consecutively referred for evaluation of CRVO. The correlation between visual acuity and oxygen saturation in the larger retinal vessels, and the predictive value of the oxygen saturation for visual prognosis after three monthly intravitreal injections with anti-VEGF medication were studied.

METHODS. Retinal oximetry was performed in 91 patients consecutively referred for specialist evaluation of CRVO. The correlation between oxygen saturation in larger retinal vessels and visual acuity at the primary examination and the predictive value of oxygen saturation for visual prognosis after three monthly intravitreal injections with anti-VEGF medication were studied.

RESULTS. At referral, the oxygen saturation in larger retinal vessels of the affected eye was significantly higher in arterioles (100.7 ± 1.4% vs. 96.3 ± 0.6%) and significantly lower in venules (37.8 ± 2.6% vs. 58.2 ± 1.3%) than in the unaffected eye (P < 0.001 for both comparisons). Best-corrected visual acuity (BCVA) showed a significant negative correlation with the oxygen saturation in retinal arterioles (P = 0.002) and a significant positive correlation with the saturation in retinal venules (P = 0.013). Multiple linear regression showed that BCVA, but not oxygen saturations, contributed significantly to predicting visual outcome after three monthly intravitreal injections with VEGF inhibitor.

CONCLUSIONS. The correlation between retinal oxygen saturation and BCVA at the time of diagnosis of CRVO may help understanding hemodynamic and visual changes in the acute stages of the disease. However, retinal oximetry cannot replace measures of retinal function as a predictive parameter for the visual outcome in CRVO after three monthly intravitreal anti-VEGF injections.

Keywords: retinal vein occlusion, retinal oxygen saturation, anti-VEGF medication

Materials and Methods

Patients

Ninety-one patients with newly diagnosed CRVO on one eye examined successively at the Department of Ophthalmology, Aarhus University Hospital, between February 1, 2013 and June 1, 2016 were studied. The patients had been referred from private practice ophthalmologists or had been diagnosed in the department after referral for other ocular diseases. The age of the patients (in years) was (mean ± SD, range) 70.8 ± 12.4, 28 to 96, n = 91, and the nearest subjective estimate of symptom duration where available (in months) was (mean ± SD, range) 2.3 ± 1.4, 0.5 to 6, n = 51. Relevant previous systemic and ophthalmological diseases are shown in Table 1.
The Regional Scientific Ethics Committee approved the study. The patients had given their informed written consent to participate, and the study followed the tenets of the Declaration of Helsinki.

Ophthalmologic Examination

The patients were subjected to a routine ophthalmologic examination, including a measurement of best-corrected visual acuity (BCVA) by Early Treatment Diabetic Retinopathy Study (ETDRS) standards. Using this technique, visual acuity is expressed on a scale between 0 and 100 corresponding to visual acuities between 0.02 and 2.0, and the values can be handled arithmetically without logarithmic transformation. The pupils were dilated using tropicamide 1% (Alcon, Copenhagen, Denmark) and phenylephrine 10% (Amgros I/S, Copenhagen, Denmark) eye drops. Subsequently, the patients were subjected to slit-lamp examination, +90 diopter (D) lens biomicroscopy of the fundus, 60° fundus photography (Canon CF 60Z; Canon, Amstelveen, the Netherlands), optical coherence tomography (OCT) scanning (Cirrus HD-OCT; Carl Zeiss Meditec, Dublin, CA, USA) using the macular cube 512 × 128 scan pattern in the CRVO eyes for each person.

On the basis of the clinical examination the diagnosis of CRVO was made in cases where the patient had noticed sudden unilateral visual loss or when characteristically morphologic lesions were observed, such as venous congestion, hemorrhages, and edema at and around the optic disk and when no evidence suggested other causes of the findings than CRVO.

Retinal Oximetry

Oximetry was performed using the Oxymap equipment (model T1; Oxymap, Reykjavik, Iceland). The system consists of a Topcon 50° fundus camera (Topcon TRC-50DX; Topcon Corporation, Tokyo, Japan), which splits the image from the ocular fundus into two images containing reflected light at 570 and 600 nm. On images recorded with the optic disk in the center specialized software automatically detects the retinal vessels, and the absorbance of light in the vessels and the perivascular retina at the two wavelengths are used to calculate the oxygen saturation in the larger clearly discernible retinal vessels.

The automatic software also displays the oxygen saturation in retinal vessels as pseudocolors as shown in Figure 1.

Treatment

The treatment was initiated according to national Danish guidelines implying that patients with BCVA between 35 and 70 ETDRS letters without a neovascular response were offered intravitreal injection with VEGF inhibitor.

Treatment was omitted in nine patients who had a higher and 15 patients who had a lower BCVA than this range and in four patients who received panretinal photocoagulation because of retinal neovascularization. This left 63 patients, of whom six refused anti-VEGF treatment, thus leaving 57 patients (62.6%) to be treated. The treatment protocol consisted of three monthly intravitreal injections with anti-VEGF compound followed by controls after 1 and 4 months and subsequently monthly, where treatments were repeated pro re nata until visual acuity and/or central retinal thickness had stabilized. The first 18 patients had the three loading injections with ranibizumab 0.5 mg (Lucentis; Novartis AG, Basel, Switzerland). National recommendations for first choice treatment changed during the period so that the last 37 patients had the three loading injections with aflibercept 2 mg (Eylea; Bayer AG, Leverkusen, Germany).

Follow-Up

The examination program was repeated 3 (n = 51) and 6 (n = 34) months, respectively, after the first treatment (~1 and 4
months after the last treatment). None of the patients received more than the first three loading injections during this follow-up period, whereas eight patients received repeated injections later. At the 1 and 4 months follow-up, only BCVA and central retinal thickness (CRT) from the OCT scans were recorded for the analysis.

Data Analysis

The oxygen saturations were extracted from the disk-centered image of both eyes from all patients using the inbuilt software (Oxymap Analyzer version 2.5.2, V2). The procedure has been described previously, and an example of the oximetry examination is shown in Figure 1.

Briefly, an inbuilt marking tool was used to define a circle with the best fit to the disk margin. Subsequently, two larger circles concentrically with the disk limiting circle were defined, an inner circle with a 15-pixel larger radius and an outer circle with 1-disk diameter larger radius. Within these two circles the saturations and diameters were collected from the longest unbranched part of eight blood vessel segments from the major arterioles and venules to the upper and lower temporal (UT, LT) quadrants. The average saturation of respectively the four nasal (UN, LN), and the upper and lower temporal (UT, LT) quadrants. The average saturation of arterioles and venules were calculated to result in an overall arteriovenous (A-V) saturation difference therefore significantly higher \( (P < 0.0001) \) than in the unaffected eye.

Figure 2 shows that in the CRVO BCVA correlated (Fig. 2A) negatively with the arterial oxygen saturation \( (P = 0.002) \), (Fig. 2B) positively with the venous oxygen saturation \( (P = 0.013) \), and (Fig. 2C) negatively with the A-V saturation difference \( (P = 0.0005) \), whereas the central retinal thickness (CRT) correlated (Fig. 2D) positively with the arterial oxygen saturation \( (P = 0.003) \), (Fig. 2E) negatively with the venous oxygen saturation \( (P < 0.001) \), and (Fig. 2F) positively with the A-V saturation difference \( (P < 0.0001) \).

Table 3 shows that 1 month after the last injection BCVA had increased significantly \( (P < 0.0001) \) and CRT decreased significantly \( (P = 0.0003) \), whereas after 4 months BCVA had decreased to not differ significantly from before treatment \( (P =

<table>
<thead>
<tr>
<th>Variable</th>
<th>CRVO Eye</th>
<th>Unaffected Eye</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sat-A % (mean ± SEM, ( n ))</td>
<td>100.7 ± 1.4, 83</td>
<td>96.3 ± 0.6, 74</td>
<td>0.001</td>
</tr>
<tr>
<td>Sat-V % (mean ± SEM, ( n ))</td>
<td>37.8 ± 2.6, 85</td>
<td>58.2 ± 1.3, 74</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>AV-Sat difference % (mean ± SEM, ( n ))</td>
<td>61.6 ± 2.7, 83</td>
<td>38.1 ± 1.1, 74</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>OEF (mean ± SEM)</td>
<td>0.61 ± 0.03, 83</td>
<td>0.40 ± 0.01, 74</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Statistics

All statistical analyses were performed using STATA (version 14.2; College Station, TX, USA). Probability plots were used to ensure that data was normally distributed. Paired \( t \)-tests were used to test differences between the two eyes. Pearson’s test was used to test the correlation between oxygen saturation and both BCVA and CRT at baseline. Multiple linear regressions were used to test whether the explanatory variables arterial and venous oxygen saturation, and age as continuous variables and sex, smoking habit, type of anti-VEGF compound, and cardiovascular disorder as categorical variables could predict BCVA or CRT at the two follow-up examinations.

Results

The saturation values in the studied patients at baseline are shown in Table 2. It appears that in eyes affected by CRVO the oxygen saturation in the arterioles was significantly higher \( (P = 0.001) \), in the venules significantly lower \( (P < 0.0001) \), and the arterio-venous (A-V) saturation difference therefore significantly higher \( (P < 0.0001) \) than in the unaffected eye.

Figure 2. The oxygen saturation at baseline in arterioles (upper row), venules (middle row) the arterio-venous saturation difference (bottom row), as a function of BCVA (A–C) and CRT (D–F). The dotted lines most distant from the regression lines indicate the 95% reference ranges and the proximally located dotted lines the 95% confidence intervals.
The study confirms results from previous studies that the oxygen saturation in larger retinal vessels is reduced in patients with CRVO. However, the study also extends these studies by verifying a higher oxygen saturation in retinal arterioles, which was suggested in a previous study but could not be confirmed due to lack of statistical power. The results are also in agreement with findings of increased arterial oxygen saturation in patients with peripheral retinal ischemia secondary to proliferative diabetic retinopathy that correlates with the severity of peripheral retinal ischemia. This observation can be explained as a result of reduced oxygen exchange between the adjacent positioned central retinal artery and vein in the optic nerve during increased retinal blood flow, which might be the case in the studied CRVO patients if the occluded vessel had recanalized. In the eyes affected by CRVO the variation in the oxygen saturation was much higher in retinal venules than in arterioles which confirms the results of a previous study. This may indicate that the venous oxygen saturation is related to the individual factors, such as the severity of ischemia and hypoxia in the retinal area affected by the occlusion, whereas the arterial oxygen saturation is a more unspecific response to the presence of a venous occlusion as such. An investigation of this issue should be the subject of a future study. The study is the first to include a sufficient number of CRVO patients to document a correlation between the oxygen saturation in retinal vessels and visual acuity and central retinal thickness. This indicates that the oxygen saturation in the larger retinal vessels may be a marker of the degree of retinal damage at the time of diagnosis of CRVO. Because the arterial and the venous saturations showed opposite correlations with both BCVA and CRT, the correlations between the A-V saturation difference and both BCVA and CRT were the same as those of the arterioles, however with a steeper slope. From the variation in the regression of this parameter it can be calculated that the A-V saturation difference can predict the visual acuity resulting from the occlusion with a precision of 14% and probably reflects that patients with more severe visual impairment have more reduced retinal flow to result in increased extraction of oxygen. Therefore, the changes in oxygen saturation in patients with CRVO may be a significant indicator of the severity and extent of the retinal area affected by the disease and may potentially contribute to our understanding of the pathophysiology of the disease. The findings confirm previous studies showing that the visual acuity is increased and CRT reduced after anti-VEGF treatment of CRVO. The observed positive predictive value of visual acuity at the time of diagnosis may be due to a better potential for recovery in cases where the retina is less affected by ischemia. The oxygen extraction fraction describes the relation between metabolism and blood supply and the difference observed between the affected and the nonaffected eyes illustrates the efforts of metabolically starving retinal cells to extract oxygen from the impaired blood supply in CRVO. This may be an important parameter for future monitoring patients with vaso-occlusive conditions in the retina.

The finding of a positive predictive value of treatment with aflibercept as compared with ranibizumab after visual acuity had been removed from the multiple regression supports...
differences in the effects of the two compounds per injection during the first year of treatment20,21 and may indicate that the patients treated with ranibizumab should have received more injections. However, the lack of predictive value of the oxygen saturation for visual acuity 1 and 4 months after loading treatment indicates that the association between visual acuity and oxygen saturation disappeared over time. The loss of patients for follow-up may have reduced the statistical power underlying this conclusion, but it was confirmed by supplementary correlation analyses between BCVA and oxygen saturation at the follow-up examinations (not shown). The finding may be due to selective effects of anti-VEGF treatment on either BCVA or CRT, or that the spontaneous evolution of the two parameters are independent. This suggests that the correlation between oxygen saturation and visual acuity at the time of diagnosis does not reflect a causal relation between these two factors, but that these are independent effects of the changes in retinal blood flow in CRVO.

The lack of predictive value of the retinal oxygen saturation for the visual prognosis after anti-VEGF treatment in CRVO is opposite to findings in diabetic macular edema where the arterial oxygen saturation has been shown to be predictive for visual outcome after treatment.22 This underlines the differences in etiology and pathophysiology of retinal vascular diseases with similarities in the types of morphologic lesions.

Altogether, the results of the study support evidence that retinal function and not the degree of ischemia or hypoxia is the best predictive parameter for the visual prognosis in CRVO. Therefore, retinal oximetry cannot replace measures of retinal function as a predictive parameter for the visual outcome in CRVO after three monthly intravitreal anti-VEGF injections. However, the correlation between retinal oxygen saturation and both visual acuity and central retinal thickness at the time of diagnosis of CRVO may help understanding hemodynamic and visual changes in the acute stages of the disease.

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References


