Effects of Intravitreal Dexamethasone Implants on Retinal Oxygen Saturation, Vessel Diameter, and Retrobulbar Blood Flow Velocity in ME Secondary to RVO

Katharina Eibenberger,1 Leopold Schmetterer,2–6 Sandra Rezar-Dreindl,1 Piotr Wozniak,2 Reinhard Told,1,2 Georgios Mylonas,1 Christoph Krall,7 Ursula Schmidt-Erfurth,1 and Stefan Sacu1

1Department of Ophthalmology, Medical University of Vienna, MUV, Vienna, Austria
2Department of Ophthalmology, Waehringer Guertel 18-20, 1090 Vienna, Austria; stefan.sacu@meduniwien.ac.at.
3Center for Medical Physics and Biomedical Engineering, Medical University of Vienna, Vienna, Austria
4Singapore Eye Research Institute, Singapore
5Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore
6Ophthalmology and Visual Sciences Academic Clinical Program, Duke-NUS Medical School, Singapore
7Department of Medical Statistics, Medical University Vienna, MUV, Vienna, Austria

Correspondence: Stefan Sacu, Medical University of Vienna, Department of Ophthalmology, Waehringer Guertel 18-20, 1090 Vienna, Austria; stefan.sacu@meduniwien.ac.at.
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Purpose. To investigate the effects of intravitreal 0.7 mg dexamethasone implants (Ozurdex) on arterial and venous oxygen saturation, retinal vessel diameter, and retrobulbar blood flow velocity in patients with macular edema (ME) due to retinal vein occlusion (RVO).

Methods. This prospective, nonrandomized clinical trial included 40 eyes of 40 patients with ME due to RVO. Measurements of arterial and venous oxygen saturation and retinal vessel diameters were performed using the Dynamic Vessel Analyzer. The main outcome measure was the retinal arteriovenous oxygen difference, calculated as the difference between arterial and venous oxygenation. Color Doppler imaging was performed for measuring peak systolic velocity (PSV), end diastolic velocity (EDV), and resistive index (RI) in ophthalmic artery (OA), central retinal artery (CRA), and posterior ciliary arteries (PCAs). Follow-up was monthly for 6 months following an initial dexamethasone implant injection. As statistical analysis, a mixed model was performed to investigate the effect treatment.

Results. The arteriovenous oxygen difference showed a significant increase (P < 0.01). Arterial oxygenation and vessel diameter did not respond to the treatment (P > 0.05), while the venous oxygen saturation and diameter decreased significantly (P < 0.01) compared to baseline. The retrobulbar blood flow velocities PSV, EDV, and RI showed no change in the OA, CRA, and PCA (P > 0.05).

Conclusions. In patients with RVO, intravitreal dexamethasone treatment leads to an increase in arteriovenous oxygen saturation difference indicating improved retinal oxygenation. Arterial oxygenation and vessel diameter showed no response, whereas venous oxygenation and vessel diameter decreased after treatment.

Keywords: retinal vein occlusion, retinal oxygen saturation, retinal vessel diameter, retrobulbar blood flow velocity, dexamethasone intravitreal implant

Retinal vein occlusion (RVO), occurring in branch (BRVO) or central veins (CRVO), is a retinal vascular disease affecting middle-aged to elderly people. Clinically, it is associated with retinal hemorrhage, dilated retinal vessels, optic disc edema, cotton wool spots, and macular edema (ME), the latter being the most common complication leading to visual impairment. The pathogenesis of ME in RVO is not completely understood, but contributing factors such as obstructed veins present a higher intraluminal pressure, which causes impaired venous blood flow velocity, variable retinal capillary nonperfusion and retinal hypoxia. The first approach of treating ME in RVO was laser photocoagulation (LP) in the mid-1990s, which induces scarring of ischemic tissue to relieve hypoxic stress. In CRVO, LP did not improve vision, whereas in BRVO vision improved and ME resolved long-term. Since the introduction of anti-VEGF agents, quick vision improvement and ME reduction in both BRVO and CRVO could be demonstrated for ranibizumab (Lucentis; Genentech, Inc., South San Francisco, CA, USA) and aflibercept (VEGF Trap-Eye, Eylea; Regeneron, Tarrytown, NY, USA). Besides anti-VEGF treatment, another therapeutic option was introduced for treating ME in RVO patients, an intravitreal 0.7-mg dexamethasone implant (Ozurdex; Allergan, Inc., Irvine, CA, USA). The drug-copolymer complex allows a gradual release of dexamethasone into the vitreous over several months. Studies have analyzed the efficacy of the dexamethasone implant regarding the functional and morphologic outcome in RVO. A 15-letter improvement up to 90 days after dexamethasone implant application was observed in patients with RVO compared with the control group. The rationale for steroid use in ME related to uveitis, diabetic retinopathy, or RVO is the potential to intervene in inflamma-
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The basic mechanism is inhibition of pro-inflammatory mediators such as prostaglandins, leukotrienes, and several other ocular cytokines. Furthermore, steroids are able to reduce vascular permeability by stabilizing endothelial cell tight junctions. Several studies have examined the effect of anti-VEGF therapies or triamcinolone on intraocular cytokines, oxygenation and retinal blood flow in uveitis, diabetic retinopathy, AMD, or RVO. Treatment with intravitreal corticosteroids causes a change within the inflammatory cascade of intraocular cytokines. Many of these cytokines also exhibit vasomotor effects and may therefore influence retinal oxygenation, vessel diameters, and blood flow.

In the present study, we investigated the effects of intravitreal dexamethasone implants on retinal oxygen saturation and retinal vessel diameter in eyes with ME secondary to BRVO or CRVO. In addition, we assessed retrobulbar blood flow velocity in the ophthalmic artery (OA), central retinal artery (CRA), and posterior ciliary arteries (PCAs).

**MATERIALS AND METHODS**

The study was approved by the local ethics committee of the Medical University of Vienna (EK 1110/2012) and the Austrian Federal Office for Safety and Health Care. It was registered at clinicaltrialsregister.eu (Eudra CT Nr: 2012-000800-13). The study adhered to the tenets of the Declaration of Helsinki, and all patients gave written informed consent before inclusion. Part of this study has been published earlier.

A total of 40 patients with ME secondary to BRVO and CRVO were included in this prospective, nonrandomized clinical trial. Patients were selected at the Department of Ophthalmology, Medical University of Vienna, Austria, between February 2013 and April 2014. Inclusion criteria were decreased visual acuity (VA) and ophthalmic evidence of ME with increased macular thickness (>300 μm in central subfield) in optical coherence tomography (OCT) due to RVO. Female patients with a childbearing potential had to have a negative urine pregnancy test before they could participate in the study. Patients with former intravitreal anti-VEGF treatment would be included if the last treatment was more than 3 months before the recruitment. Patients were excluded if any ocular disease was present that in the opinion of the investigator would prevent 15-letter visual improvement, such as severe macular ischemia seen in fluorescein angiography at baseline (BSL). Furthermore, patients with any other ocular disease causing ME or neovascularization (NV) were excluded. A history of glaucoma, pars plana vitrectomy, aphakia, anterior chamber lens or significant cataract, any ocular infection, or presence of uncontrolled systemic disease were also exclusion criteria.

All patients meeting the inclusion criteria received an intravitreal injection of a sustained-release dexamethasone implant (Ozurdex; Allergan, Irvine, CA, USA) under sterile conditions following national guidelines. Follow-up visits were scheduled 1 week after treatment (initial and retreatment) and monthly up to month 6. After month 4, patients were eligible for retreatment if a decrease in best-corrected visual acuity (BCVA) and an increase in central retinal thickness (CRT) (>50 μm compared to last visit) was evident.

IOP increase was treated with topical IOP-lowering drugs, and NV of disc, retina, iris, or elsewhere was treated with pan-retinal photocoagulation. The following was performed at each study visit; a complete ophthalmic examination including 4-m ETDRS BCVA assessment, slit-lamp examination, indirect ophthalmoscopy, and applanation tonometry. CRT was assessed, using spectral-domain OCT (SD-OCT) (Spectralis SD-OCT, software version 1.5.2.0; Heidelberg Engineering, Dossenheim, Germany) volume scan (20° × 20°, 49 frames, high resolution) at all study visits. In addition, dynamic vessel analysis (Dynamic Vessel Analyzer [DVA]; IMEDOS, Jena, Germany) for retinal vessel diameter and oxygen saturation measurements and color Doppler imaging (Vivid F Pro; GE Vingmed Ultrasound, Horten, Norway) for retrobulbar blood flow assessments were performed at all visits. A wide-field fluorescein angiography (Optomap P200; Optos plc, Dunfermline, UK) for assessing macular and peripheral retinal status (leakage due to ME, retinal ischemia, or NV) and Optos microperimetry (Spectral OCT/SLO; Optos, Inc., Malborough, MA, USA) pattern grid square 7 × 7 with a presentation time of 200 microseconds and a time interval of 1.5 seconds for assessing central retinal sensitivity (CRS) were performed at baseline and at 1-, 3-, and 6-month follow-up visits.

At all visits patients received dilating eye drops: tropicamide 1% (Mydråttum; Agepha, Söding, Austria) and phenylephrine 2.5% (prepared by in-house pharmacy) before examination at all visits.

**Dynamic Vessel Analyzer**

The DVA is a noncontact device in which a fundus camera (FF450; Carl Zeiss Meditec AG, Jena, Germany), including a dual wavelength transmission filter and a charge-coupled device camera, measure the arterial and venous oxygen saturation as well as retinal vessel diameters.

Two monochromatic fundus images of the retinal vessels are taken for measuring the oxygen saturation using light with a wavelength of 610 nm and 548 nm. The contrast of arterial and venous vessels is optimal at 610 nm since oxygenated and deoxygenated hemoglobin have different light absorption levels, whereas at 548 nm the absorption is equal in both vessel systems. Oxygenation of arteries and veins can be determined based on these two images. The arteriovenous oxygen difference is calculated as the difference between arterial and venous oxygen saturation.

Arterial and venous vessel diameters are detected by means of a vessel-analyzing software using adaptive algorithms to delineate vessel borders. All arterial and venous vessels are automatically selected by the device software at BSL and are saved for follow-up visits. Temporal vessels between 1 and 2 disc diameters from the margin of the optic disc were used for the measurement of retinal vessel diameters or oxygenation.

**Color Doppler Imaging (CDI)**

Retrobulbar blood flow velocity was measured in the OA, CRA, and PCA using a Vivid 7 Pro color ultrasound device). The retrobulbar blood flow velocities are measured using a combined transducer with 7.0 MHz for B-mode (intensity: 40 mW/cm²) and 5.0 MHz for pulsed Doppler (intensity: 25 mW/cm²). Ultrasonic gel (methylcellulose 2%) was administered on the eyelid to reduce transmission interference before placing the transducer on the closed eye. The peak systolic velocity (PSV) and end diastolic velocity (EDV) of each vessel (OA, CRA and PCAs) were measured as described by Lieb et al. Furthermore, the resistive index (RI) is calculated as RI = (PSV – EDV)/PSV and the time-averaged maximum velocity (TAm) as the mean time flow of the spectral outline.

**Outcome Variables and Statistical Analysis**

AV oxygen difference was the main primary outcome measure. Secondary outcome measures included VA, CRS, and CRT,
arterial and venous oxygenation, and vessel diameters, as well as the blood flow velocities of OA, CRA, and PCAs.

Adverse events from the Ozurdex implant or RVO disease such as a raise in IOP or NV occurrence were monitored at every visit.

With a sample of 40 patients, a mean change of the AV oxygen difference by 0.5 standard deviations of the difference could be detected with 80% power. Statistical analysis was performed in programming environment R 3.0.2 under R Studio 0.98.482 (RStudio, Boston, MA, USA). Nominal data such as baseline characteristics are presented in frequency and percentage. All categorical values were checked for normal distribution and are expressed as mean value ± standard deviation. A P value < 0.05 was considered statistically significant.

A mixed linear model was applied to the main outcome measure, AV oxygen difference, to investigate the response of intravitreal dexamethasone treatment on the total study population. Time was measured since last treatment, and a quadratic term in time was also included to model regression to the baseline value. The results of the secondary outcomes were statistically analyzed in a descriptive manner; therefore, no correction for multiple testing was performed. Mixed models were used to investigate arterial or venous oxygen saturation and vessel diameter of the study population and for each subgroup separately (BRVO, CRVO). Also to investigate the blood flow velocity including peak systolic velocity (PSV), end diastolic velocity (EDV), the RI, and TAmax in all arteries (OA, CRA, PCAs), mixed linear models were used, considering total time since first treatment to model long-term trends. PSV, EDV, and TAmax were log-transformed.

Furthermore, a mixed model analysis was used for correlation of AV oxygen difference to BCVA or CRS or CRT and to venous diameter, and for correlation of venous oxygen saturation to venous vessel diameter.

The results of statistical analysis using mixed models are reported as P value, regression coefficient (b), and 95% confidence interval.

**RESULTS**

Twenty-five male and 15 female patients were included in this study with a mean age of 69.5 ± 10.6 years (range, 49 to 89 years). Baseline VA was 65.3 ± 14.4 letters, CRS was 10.4 ± 3.5 dB, and CRT was 533.2 ± 150.9 μm. At the last visit, improvement of all functional parameters was observed; VA increased to 71.7 ± 16.1 letters (P < 0.01) and CRS to 11.1 ± 3.2 dB (P = 0.02). Furthermore, CRT decreased to 501.9 ± 85.0 μm (P < 0.01).

Twelve patients with BRVO and nine with CRVO were treatment naïve. Seven patients with BRVO and three with CRVO were treated with intravitreal anti-VEGF injections (either ranibizumab or bevacizumab) more than 3 months before inclusion. The remaining six with BRVO and three with CRVO had received additional photocoagulation to anti-VEGF treatment more than 3 months before inclusion.

The Table shows the demographic characteristics, functional and anatomical results of the total study population, and BRVO and CRVO subgroups at baseline.

Overall 31 out of 40 patients required retreatment with Ozurdex; 22 patients at month 4 (BRVO: n = 14; CRVO: n = 8), eight at month 5 (BRVO: n = 5; CRVO: n = 3), and one at month 6 (BRVO: n = 1). A raise in IOP occurred in 12 patients (BRVO: n = 6; CRVO: n = 6) on average 3 months after initial treatment. IOP increased above 30 mm Hg in 20% of the patients. Nine patients were treated with a monotherapy antiglaucoma eyedrop (carbonic anhydrase inhibitors), whereas three patients had combined antiglaucoma eyedrops. One patient required pan-retinal photocoagulation due to neovascularization of the optic disc at month 4.

**Oxygenation and Diameter of Retinal Vessels**

The main outcome measure, AV oxygen difference, showed a statistically significant trend in the total study population (BSL: 18.0% ± 7.9%; month 6: 19.3% ± 8.2%; see Fig. 1). We observed a significant linear increase (P = 0.008; b: 0.061; confidence interval [CI]: 0.544, 3.578) resulting in a peak at month 2 and a quadratic decrease (P = 0.003; b: 0.056; CI: −0.834, −0.177). Furthermore, we found no significant correlation of AV oxygen difference to the functional parameters VA and CRS (both P > 0.05). A significant negative correlation could be demonstrated between AV oxygen difference and CRT (P = 0.004; b: −0.009; CI: −0.015, −0.003).

The arterial oxygenation (BSL: 95.7% ± 3.5%, month 6: 94.3% ± 3.0%, see Fig. 2) showed no statistical trend in the total study population (P > 0.05). A similar result was observed in both subgroups (BRVO and CRVO: P > 0.05). On the opposite side, the results of the venous oxygenation showed a linear decrease (P = 0.001; b: 2.543; CI: −4.047, −1.039) and a quadratic increase (P = 0.001; b: 0.566; CI: 0.243, 0.890) in the total study population (BSL: 77.6% ± 8.0%, month 6: 75.0% ± 8.6%, see Fig. 3). A similar response was only observed in the CRVO group (P < 0.01), whereas no such effect could be observed in the BRVO group (P > 0.05).

At BSL, mean arterial diameter was 105.1 ± 16.9 μm, and no change was found during follow-up (month 6: 100.8 ± 18.5 μm; P > 0.05, see Fig. 4). Furthermore, no response to treatment was observed for the arterial diameter when looking at each subgroup (all P > 0.05). The venous vessel diameter showed a linear decrease (P = 0.001; b: −5.845; CI: 9.154, 2.533) and a quadratic increase (P = 0.001; b: 1.228; CI: 0.539, 1.918) in the total study population (BSL: 151.8 ± 20.3 μm, month 6: 137.5 ± 17.0 μm, see Fig. 5) and the CRVO subgroup (P < 0.01), while no such response was found for the BRVO subgroup (P > 0.05). A positive correlation was observed for the venous diameter to the venous oxygenation for the total study population (P = 0.001; b: 0.103; CI: 0.045, 0.162), whereas a negative correlation to the arteriovenous difference was observed (P = 0.001; b: −0.101; CI: −0.159, −0.043).

**Blood Flow Measurements of Retinal Vessels**

In the OA, the PSV (BSL: 30.9 ± 11.6 cm/s; month 6: 33.0 ± 10.6 cm/s) and EDV (BSL: 7.0 ± 3.0 cm/s; month 6: 7.3 ± 3.7 cm/s) showed no change over time (PSV: P = 0.72; b: 0.003; CI: −0.013, 0.019; EDV: P = 0.72; b: −0.005; CI: −0.024, 0.014). Likewise, for the RI (BSL: 0.8 ± 0.3 cm/s; month 6: 0.8 ± 0.1 cm/s) and TAmax (BSL: 15.3 ± 5.6; month 6: 16.5 ± 6.4 cm/s) no change was observed over time (RI: P = 0.23; b: 0.002; CI: −0.001, 0.005; TAmax: P = 0.62; b: 0.004; CI: −0.013, −0.022).
In the CRA, the PSV (BSL: 11.4 ± 4.0 cm/s; month 6: 10.4 ± 2.7 cm/s) and EDV (BSL: 3.2 ± 1.7 cm/s; month 6: 3.2 ± 1.2 cm/s) showed no change over time (PSV: $P = 0.46$; b: −0.006; CI: −0.024, 0.011; EDV: $P = 0.16$; b: 0.017; CI: −0.007, 0.04). Likewise, the RI (BSL: 0.7 ± 0.1 cm/s; month 6: 0.7 ± 0.1 cm/s; $P = 0.04$; b: −0.009; CI: −0.015, −0.005) and $T_{A_{\text{max}}}$ (BSL: 6.6 ± 2.6 cm/s; month 6: 6.4 ± 1.6 cm/s; $P = 0.78$; b: 0.003; CI: −0.015, 0.02) showed no or only marginal change over time.

In the PCA, no significant difference over time was observed for the blood flow velocity measurements PSV (BSL: 13.7 ± 3.7 cm/s; month 6: 13.8 ± 3.5 cm/s; $P = 0.31$; b: 0.008; CI: −0.007, 0.022) and EDV (BSL: 4.5 ± 0.8 cm/s; month 6: 4.2 ± 1.0 cm/s; $P = 0.99$; b: 0.0; CI: −0.013, 0.013). Furthermore, the RI (BSL: 0.7 ± 0.09 cm/s; month 6: 0.7 ± 0.08 cm/s) and $T_{A_{\text{max}}}$ (BSL: 8.2 ± 1.7 cm/s; month 6: 8.2 ± 1.9 cm/s) did not change over time (RI: $P = 0.30$; b: 0.002; CI: −0.002, 0.006; $T_{A_{\text{max}}}$: $P = 0.43$; b: 0.005; CI: −0.008, 0.018).

**Discussion**

In our study, we evaluated the response of retinal oxygen saturation, retinal vessel diameter, and retrobulbar blood flow velocity to intravitreal dexamethasone treatment for ME in RVO. The functional and morphologic improvement confirms previous studies assessing the efficacy and safety of dexamethasone implants.12,13 In our study, the rate of IOP elevation was...
30%, which is similar to the literature, ranging from 16% to 40%.

At baseline, the arteriovenous oxygen difference was approximately 18.0% ± 7.9% in our patients with BRVO and CRVO. Eliasdottir et al. observed an increased AV oxygen difference of 65% ± 11% at initial presentation, since only acute CRVO patients were evaluated. Especially in RVO, a difference in retinal oxygen saturation was found in acute and chronic RVO. The venous oxygen saturation in acute RVOs is markedly decreased, whereas normalization probably due to reperfusion was observed in chronic RVO. During the follow-up, we observed an increase in AV oxygen difference 2 months after Ozurdex treatment in our study. In addition, we found a negative correlation between the AV oxygen difference and CRT, which suggests that the oxygen extraction is lower in edematous retinas than in nonedematous retinas.

The baseline value of the arterial oxygenation, 95.7%, was comparable to other studies on RVO. Furthermore, we observed no response of arterial oxygenation to treatment similar to Traustason et al. who found no change in arterial oxygenation in CRVO treated with intravitreal ranibizumab over time.

In our study, a decrease of venous oxygen saturation was observed in the total study population and the CRVO subgroup. When examining the effect of intravitreal ranibizumab treatment in CRVO, Traustason et al. described reduced oxygen levels in veins at baseline and found a significant increase in affected venous oxygen saturation under treatment.
Furthermore, our venous oxygenation levels differ from those found in other studies. We measured oxygen levels of 77.6% ± 8.0% at baseline and 75.0% ± 8.6% at month 6, whereas Hardarson et al. found reduced oxygen saturation in affected veins (49% ± 12%) compared to unaffected veins (65% ± 6%) in patients with CRVO. In another paper, Hardarson et al. described a broad range for venous oxygenation (range, 12% to 93%) in occluded veins, which they attributed to the different levels of severity.

However, these results are not directly comparable owing to the different methods used. Hardarson et al. analyzed single affected veins, whereas we calculated a mean value of affected and unaffected vessels for the whole retina. In these studies, a spectrophotometric retinal oximeter takes several pictures at two wavelengths (605 nm and 586 nm) and automatically delineates the vessels. Compared to our measurement technique, the spectrophotometric analysis measures the reflected light of all vessels and the surrounding retina to calculate the oxygenation.

The arterial diameter in the total population and both subgroups showed no change after intravitreal dexamethasone treatment. In contrast, several studies found a significant decrease in arterial diameters during anti-VEGF treatment in BRVO and AMD. In veins a significant decrease of diameters was observed in the total study population and CRVO considering treatment, whereas none was observed in BRVO. Also, Nagaoka et al. could not detect a reduction in venous diameters in BRVO treated with bevacizumab using LDV. RVO damages the retinal vascular system, thus triggering an inflammatory reaction of ocular cytokines. Furthermore, both the inflammatory cascade and vascular dysfunction interact and stimulate each other. As a result, vasodilatation and increased vascular permeability lead to leakage and edema within the retina.

Intravitreal dexamethasone intervenes at several points in this pathologic pathway. This may result from a down-regulation of intraocular cytokine production or stabilization of endothelial cell tight junctions. Therefore, dexamethasone may lead to vasoconstriction, which we observed in retinal veins only, but has been found in both retinal arteries and veins in other studies. However, it has to be considered that different agents were used in these studies. Furthermore, we observed a positive correlation of the venous diameter and venous oxygen saturation. It seems that a decrease in venous diameter also leads to a decrease in venous oxygenation.

In our study, the retrobulbar blood flow velocity parameters showed hardly any response to intravitreal dexamethasone treatment for the total population over time. Similar results for bevacizumab in BRVO and triamcinolone in CRVO showed no change in retrobulbar blood flow velocity.

One of our study’s limitations is the relatively low number of patients regarding the secondary outcome measures. We cannot present statistical significant results since the power analysis of the study was set for the main outcome measure, AV oxygen difference. Another limitation is the wide heterogeneity of the study population as patients were allowed to have received previous LP or anti-VEGF treatment. A study by Sacu et al. demonstrated a significant vasoconstriction following intravitreal ranibizumab treatment in arteries but more pronounced in veins affected by BRVO after a follow-up of 3 months. Therefore, in our study no treatment was allowed 3 months before study inclusion to minimize the effect of anti-VEGF agents and LP. Furthermore, we did not evaluate the healthy fellow eye, which could have served as a healthy control group. Furthermore, no sufficient data exist on the natural course of the disease regarding reperfusion and therefrom the improvement of retinal oxygenation and vessel diameter. Hence, an influence of natural recovery on the observed results cannot be completely ruled out.

Another limitation is the use of phenylephrine as pupil dilation, which might cause vasoconstriction in the retinal vascular systems, even after topical administration. In the present study, phenylephrine was applied in all patients at each visit. Therefore, its potential vasoconstrictive effect can be assumed a constant bias in all measurements.

The raise in intraocular pressure (on average 91 ± 50 days after initial treatment) as well as the need for pressure-lowering drugs might be further limitations of the study. Clinical examination revealed an open angle, and patients were asymptomatic. Furthermore, an elevated IOP causing distur-
bance of ocular blood flow has been found in several glaucoma studies.\textsuperscript{44,45} Several studies have analyzed the effects of IOP-lowering drugs on ocular blood flow and have found reduced IOP to be associated with a normalization of retinal flow, whereas others have found no hemodynamic change in retrobulbar blood flow.\textsuperscript{6,47} Hence, an influence of the IOP-lowering eyedrops used on retrobulbar blood flow parameters cannot be fully excluded.

**Conclusions**

In conclusion, intravitreal dexamethasone treatment leads to an increase in the retinal AV oxygen difference but does not seem to affect either the retinal arterial oxygenation or retinal arterial vessel diameters in patients treated with a dexamethasone implant because of ME due to RVO. A decreased oxygenation and vessel diameter in veins were observed with regard to treatment. Furthermore, retrobulbar blood flow velocity remained constant for all arteries. Summarizing, we observed a significant positive response in functional and morphologic characteristics following treatment with dexamethasone implants in patients with ME due to RVO.

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**References**


