

# The influence of retinal oxygen saturation and choroidal volume on postoperative outcomes in patients with epiretinal membrane

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## ABSTRACT.

**Purpose:** To investigate the effects of vitrectomy (V<sub>y</sub>) with or without same time cataract surgery and membrane plus internal limiting membrane peeling (MP+ILMP) on retinal oxygenation and choroidal volume and their role on postoperative outcome.

**Methods:** Thirty-two eyes were included in this prospective clinical study. All patients received 23 gauge V<sub>y</sub>+MP+ILMP without endotamponade. Additional cataract surgery was performed in 14 patients. Follow-up visits were scheduled at day 1, week 1, month 1 and month 3. At each visit, best corrected visual acuity (BCVA) using ETDRS charts (except at day 1), oxygenation of retinal vessels using the Oxymap T1, and optical coherence tomography (OCT, Heidelberg Spectralis) was performed.

**Results:** Mean BCVA increased significantly from 73 ± 11 letters to 77 ± 7 letters at month 3 (p = 0.02). Mean central retinal thickness (CRT) decreased from 456 ± 84 μm at baseline to 418 ± 58 μm (p = 0.01 baseline versus month 3). In the cataract surgery group, CRT was higher at month 3 than in the group without (400 ± 58 μm versus 441 ± 51 μm; p = 0.007). There was no statistically significant difference in choroidal volume or oxygenation of retinal vessels between groups (additional cataract surgery versus vitrectomy alone). Oxygenation of retinal arteries tended to decrease at day 1 followed by an increase, but the changes did not reach the level of significance (p = 0.29 baseline versus month 3). Oxygenation of retinal veins increased significantly (p = 0.02 baseline versus month 1; p = 0.04 baseline versus month 3, accordingly). There was a significant negative correlation (Spearman correlation coefficient  $r_s = -0.35$ , p = 0.047) between visual acuity and oxygenation of retinal veins at month 3. No statistically significant correlation was found between CRT and oxygenation of neither retinal arteries nor veins. Choroidal volume (CV) of the central mm did not change significantly during the study period (baseline: 0.203 ± 0.04 mm<sup>3</sup>, median: 0.206, month 3: 0.205 ± 0.04 mm<sup>3</sup>, p = 0.54). There was no statistically significant effect of choroidal volume at baseline on postoperative clinical outcomes (change in BCVA estimate [95% CI]: 7 [−76; 90], p = 0.86; change in CRT: 147 [−577; 871], p = 0.68).

**Conclusion:** Oxygen saturation may affect the visual acuity outcome but not the CRT in patients after vitrectomy for epiretinal membrane. Choroidal thickness had no statistically significant influence on the study outcomes. Further studies are needed to evaluate if the measurement of retinal oxygenation may be helpful in the decision for surgery.

**Key words:** choroidal volume – epiretinal membrane – retinal oxygen saturation

[Correction added on 30 September 2021 after first online publication: Due to a technical error, the published version was not the final accepted version. Figure 6 was originally missed out and has now been added. This has led to corrections in the Results section to include findings presented in Figure 6. In addition, in-text citation for Bek & Jørgensen 2016, Jeppesen & Bek 2017, Kim & Park 2021 and Shui et al. (2009); Li et al. (2019) in the Discussion section were not included and have now been added. These corrections are noted in the text.]

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## Introduction

Epiretinal membrane (ERM) is a non-vascular fibrocellular proliferation that develops on the surface of the internal limiting membrane (ILM), resulting in wrinkling and distortion. These changes may lead to disturbed visual function such as metamorphopsia and reduced visual acuity (VA). Macular pucker is sometimes used as a synonym for the abnormality of the vitreoretinal interface (Okamoto et al. 2009).

The criteria for the decision of the time of surgical treatment (vitrectomy combined with removal of the ERM and ILM) of this disorder include best-corrected VA (BCVA), stage of ERM on optical coherence tomography (OCT) and patients symptoms (Kinoshita et al. 2012). Although improvement in BCVA is often observed after this surgical procedure, increase in BCVA takes less time in some cases, whereas, in others, it may even take up to one year (Massin et al. 2000; Georgopoulos et al. 2008; Kishi et al. 2019). The possible reasons discussed in the literature are assumed to be due to an alteration in retinal architecture; however, other possible factors influencing the clinical outcomes, such as retinal oxygenation or choroidal volume, need to be addressed (Sín et al. 2014; Sugiura et al. 2014; Kang et al. 2017).

Vitrectomy has various mechanical and physiological effects. A reduced risk of neovascularization in the retina and a reduction of macular edema was observed (Blankenship & Machemer 1985; Hvarfner & Larsson 2006; Laidlaw 2008; Stefánsson 2009). A known consequence of vitrectomy is the stimulation of cataract formation, which is accepted as a result of increase in oxygen tension in the vitreous cavity (Holekamp et al. 2005). When the vitreous gel is replaced with less viscous saline, the transport of all molecules is facilitated, including cytokines and oxygen, (Stefánsson 2009). Oxygenation may play an important role in the regeneration of the retinal tissue, especially after mechanical tear during membrane peeling. There is only limited data available concerning oxygen saturation of retinal vessels after surgical procedures and its effect on postoperative outcomes (Lim et al. 2014; Sín et al. 2014; Šín et al. 2016; Nakano et al. 2017).

In several studies, an influence of vitrectomy and cataract surgery on choroidal thickness has been shown, maybe influenced by vitreomacular traction or other unknown reasons (Noda et al. 2014; Ohsugi et al. 2014; Pierru et al. 2014; Michalewska et al. 2015; Ahn et al. 2016; Michalewska et al. 2016; Kang et al. 2017).

Hence, in the present study, we focused especially on the course of oxygen saturation in retinal vessels and choroidal volume and their influence on the postoperative outcomes in eyes with an idiopathic epiretinal membrane. Furthermore, we evaluated the difference in morphological and functional parameters between the combination of vitrectomy and cataract surgery to vitrectomy alone.

## Methods

After explaining the nature of the study and obtaining written informed consent, 32 patients scheduled to undergo vitrectomy with removal of the ERM and dye assisted ILM peeling were included in this unmasked prospective study. All patients had clear media to enable good measurement quality. In 14 of the included patients, additional cataract surgery was performed, simultaneously. 11/32 patients were pseudophagic and 7/32 patients had a clear lens. [Corrections added on 30 September 2021 after first online publication: new sentence was added: 11/32

patients were pseudophagic and 7/32 patients had a clear lens.] The study was conducted in accordance with the tenets of the Declaration of Helsinki and approved by the Ethics Committee of the Medical University of Vienna. The measurements of retinal oxygen saturation and vessel diameters were performed at baseline, at day 1, day 7, 4 weeks and 12 weeks after surgery using the commercially available Oxymap T1. Best corrected visual acuity (BCVA) (data of day 1 not included) using ETDRS charts, central retinal thickness (CRT) and choroidal volume (CV) using a high-resolution OCT (SPECTRALIS, Heidelberg Engineering, Heidelberg, Germany) were evaluated at each study visit, accordingly. Some parts of this study are presented in further reports (Datlinger et al. 2021; Told et al. 2020).

### Retinal oximetry

Several methods evaluating oxygen saturation in retinal vessels have been introduced (Hardarson et al. 2006; Hammer et al. 2008). Spectrophotometric retinal oximetry is a non-invasive technology for the measurement of oxygen saturation in arterioles and venules. There are two commercially available systems on the market (Told et al. 2018). In our study, we performed measurements using the Oxymap T1 system. Fundus camera-based, dual-wavelength retinal oximetry (Oxymap ehf., Reykjavik, Iceland) was performed to measure retinal oxygen saturation (SO<sub>2</sub>) in major peripapillary arteries and veins, which were defined by a diameter of  $\geq 93 \mu\text{m}$  and a segment length of  $\geq 465 \mu\text{m}$ . We adhered to these thresholds as SO<sub>2</sub> results become unreliable in thin and short vessel segments (Zong et al. 2016). All study visits were scheduled in the mid-morning to exclude the possibility of circadian fluctuations in SO<sub>2</sub>. The precise oximetry technique has been described previously (Geirsdóttir et al. 2012). In brief, the oximeter records images reflected from the retina at an oxygen-sensitive (600 nm), as well as an oxygen-insensitive (570 nm) wavelength. An inverse linear relation between the optical density ratio measured at the two wavelengths and SO<sub>2</sub> is assumed (Geirsdóttir et al. 2012). Studies have shown that this retinal oximetry technique is remarkably stable with high reproducibility and repeatability of measurements in healthy subjects as well as in diseased

retinas (Hardarson et al. 2006; Hardarson & Stefánsson 2012; Pálsson et al. 2012; Yip et al. 2014; Türksever et al. 2015).

The same masked investigator performed all analyses with the built-in software (version 2.4.0). The best quality image with the ONH in its center was chosen from every patient for further analysis according to a standard protocol given by the manufacturer: Two circles of 1.5 and 3 times the optic disc diameter were created, and all vessel segments ( $\geq 93 \mu\text{m}$  diameter and  $\geq 465 \mu\text{m}$  length) between these two circles were selected. The mean SO<sub>2</sub> and mean diameter of the selected arteries and veins were then automatically analyzed. Different blood flow in vessels was taken into account because the software adjusts for artifactual SO<sub>2</sub> changes as a result of vessel width by weighing the means with the fourth power of the vessel diameter (Konno et al. 1996). The location of each vessel segment was registered according to which retinal region they belonged to (temporal and nasal section of the ring). The saturation in venules (SO<sub>2v</sub>) was subtracted from the saturation in arterioles (SO<sub>2a</sub>) to obtain the oxygen extraction (arterio-venous oxygen saturation difference).

### Choroidal volume

For the evaluation of choroidal volume (Barteselli et al. 2012; Chhablani et al. 2012), we performed Spectralis EDI-OCT (Heidelberg Engineering, Heidelberg, Germany) volume scans with at least 25 B-scans of  $20 \times 20^\circ$  centered on the fovea. The scans were then evaluated using the OCTAVO software developed by the Vienna Reading Center. An ETDRS grid was centered on the fovea. The central mm in the choroid was marked manually between Bruch's membrane and the choroidoscleral boundary. All scans in the central mm were used for the evaluation of the choroidal volume. Using the follow up function, scans were generated at the same retinal location at every visit. All measurements were performed approximately the same time to reduce diurnal variation (Tan et al. 2012).

### Surgical procedure

All 3-port 23-gauge pars plana vitrectomies were performed using an Örtli machine (Oertli instruments, Berneck, Switzerland) with a widefield viewing

system (MiniQuad XL VIT contact lens; Volk, Mentor, OH, USA) or a biom (Oculus Surgical Inc., Port St. Lucie, FL, USA). Vitreous body removal was followed by ERM and ILM removal using a microforceps, after which the ILM was stained using viewILM dye (Alchimia, Ponte San Nicola, PD, Italy). During peeling, a contact lens (Landers contact lens, Ocular Instruments Inc. Bellevue, Washington, USA) was used for visualization of the fovea in all cases. No gas or air tamponade was used in any of the included patients. [Corrections added on 30 September 2021 after first online publication: new sentence was added: No gas or air tamponade was used in any of the included patients.]

**Statistical analysis**

For qualitative variables, absolute frequencies are reported. Quantitative variables are reported as mean ± standard deviation (SD).

To analyze the differences to baseline, paired t-tests were conducted, whereas hierarchical testing was performed, starting at month 3. In case of a p-value >0.05, the testing procedure stopped.

To analyze if the oxygenation was different between the temporal and nasal vessels, we conducted paired t-tests for each time point separately. Hierarchical testing was performed, starting at day 1. In case of a p-value >0.05, the testing procedure stopped.

To analyze if the mean change from baseline in visual acuity, CRT, oxygen saturation of retinal arteries and veins, or choroidal volume differed between patients with versus without cataract surgery, ANCOVAs were calculated with cataract surgery (reference = no) and the baseline value as independent variables. Hierarchical testing was performed, starting at month 3. In case of a result-value >0.05, the testing procedure stopped. Additionally, for each group (with and without cataract surgery) separately, the mean differences to baseline with 95% confidence limits were calculated.

To analyze the correlation of visual acuity, CRT or choroidal volume with oxygen saturation of arteries or veins at the timepoint of month 3 or the correlation between peeling size and oxygen saturation of arteries or veins, respectively, at the time point of day 1, Spearman correlation coefficients were

calculated and p-values (H0: rho = 0) are reported.

To investigate the effect of the CV on postoperative outcomes, univariate linear models were calculated with the change in visual acuity, or the change in CRT, respectively, from baseline to month 3, as a dependent variable.

For the analysis of the effect of oxygen saturation of arteries and veins and the arteriovenous difference at baseline on the change in visual acuity from baseline to month 3, univariate linear models were calculated. The estimate for the slope β1 with 95% CI and the p-value (H0: β1 = 0) is reported.

Statistical analyses were carried out with R 3.6.2. The significance level was set to 0.05. Due to the exploratory character of the study, we adjusted only for multiplicity within each objective by performing hierarchical tests, not for the number of objectives.

**Results**

**Demographic data**

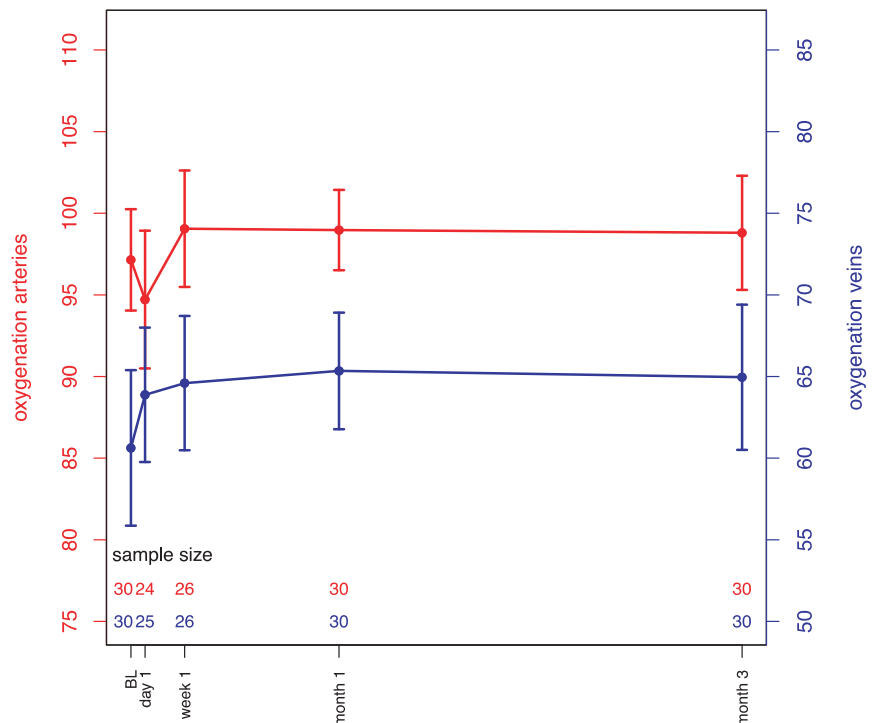
Mean age of patients was 71 ± 7 years. Fourteen of the included 32 patients (18 right eyes, 14 left eyes) received additional cataract surgery

simultaneously. Mean BCVA increased from 73 ± 11 letters to 77 ± 7 letters at month 3 (mean difference [95% CI]: 4.2 [0.7; 7.7], p = 0.02). Mean CRT decreased from 456 ± 84 μm at baseline to 418 ± 58 μm (mean difference [95% CI]: -37.9 [-66.7; -9.1], p = 0.012 baseline versus month 3; -25.1 [-49.6; -0.6], p = 0.045 baseline versus month 1), accordingly.

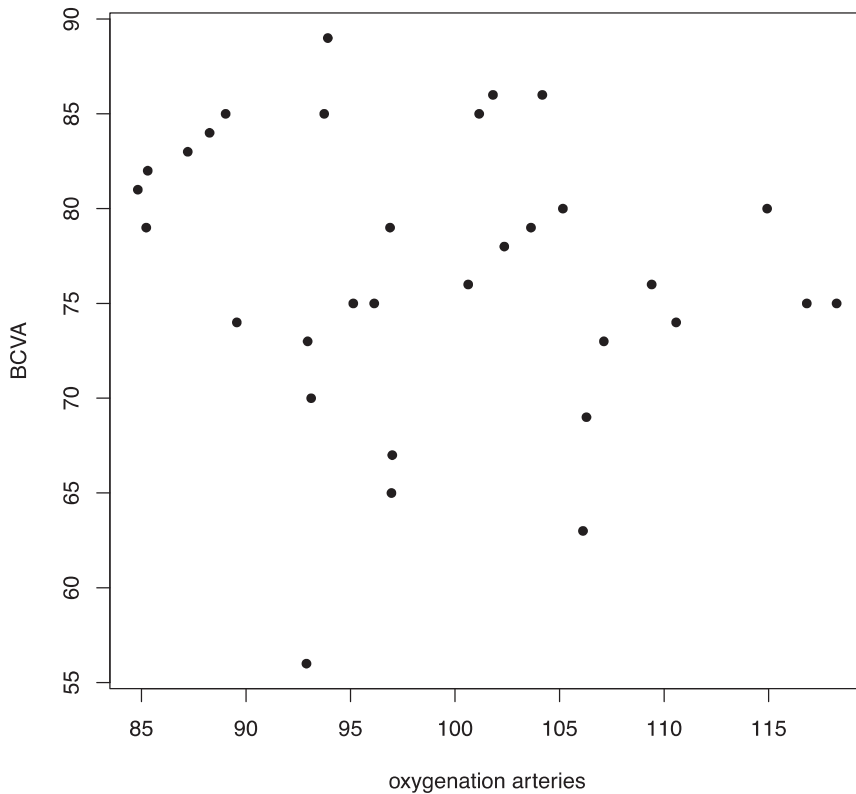
**Oxygen saturation**

Oxygenation of retinal arteries tended to decrease at day 1 followed by a tendency to increase, but the changes did not reach the level of significance (mean difference [95% CI]: 1.7 [-1.5; 4.8], p = 0.29 baseline versus month 3; Fig. 1). Oxygenation of retinal veins significantly increased compared to baseline starting at month 1 (4.7 [0.7; 8.8], p = 0.023 baseline versus month 1; 4.3 [0.3; 8.4], p = 0.036 baseline versus month 3, accordingly; Fig. 1).

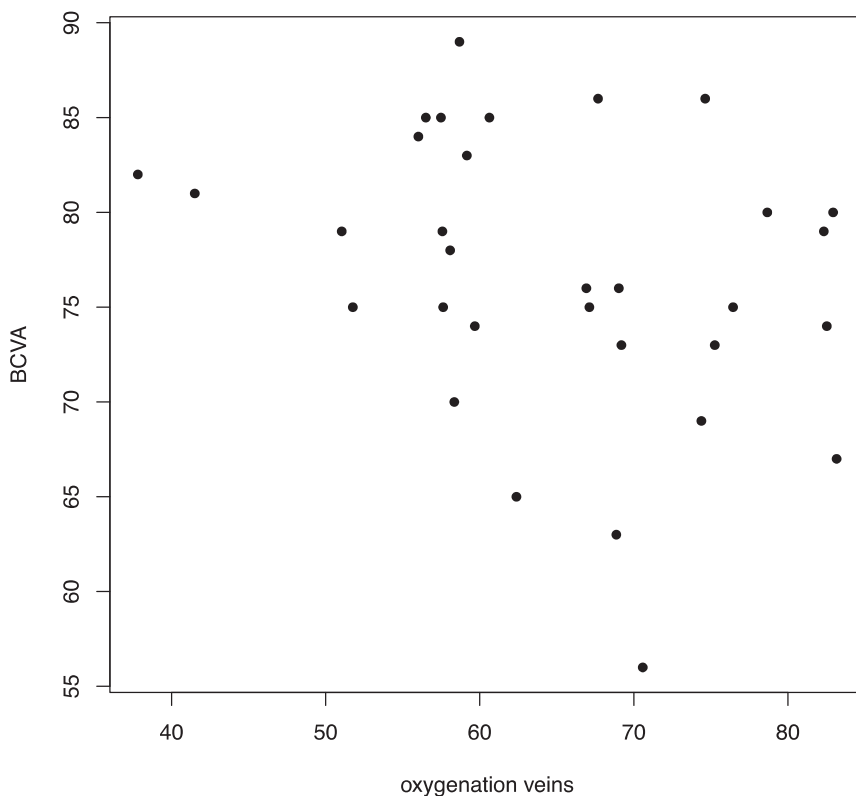
The correlation between BCVA and oxygenation of retinal arteries at 3 months was statistically not significant (spearman correlation coefficient rs = -0.22, p = 0.2). However, there was a significant negative correlation (rs = -0.353; p = 0.047) between visual



**Fig. 1.** Mean values with 95% confidence limits of oxygenation of the retinal arteries (red) and retinal veins (blue) over time. The sample size per time point is shown at the bottom of the graph. The observations of two patients with missing baseline values were excluded in this figure.



**Fig. 2.** Scatter plot of visual acuity (BCVA) and oxygenation of retinal arteries. The Spearman correlation coefficient is equal to  $-0.22$  ( $p = 0.2$ ). BCVA = best corrected visual acuity.



**Fig. 3.** Scatter plot of visual acuity (BCVA) and oxygenation of retinal veins. The Spearman correlation coefficient is equal to  $-0.35$  ( $p = 0.047$ ). BCVA = best corrected visual acuity.

acuity and oxygenation of retinal veins (Figs 2 and 3). The correlation between peeling size and oxygenation of arteries or veins at day 1 was negative, but statistically not significant (arteries:  $r_s = -0.19$ ,  $p = 0.4$ , veins:  $r_s = -0.32$ ,  $p = 0.19$ ).

Comparison between nasal and temporal vessels revealed no statistically significant differences (Figs 4 and 5).

A positive, but statistically not significant relationship between visual acuity change from baseline to month 3 and oxygen saturation in arteries at baseline was found (estimate for the slope [95% CI]:  $0.461 [-0.027; 0.95]$ ,  $p = 0.063$ ). The effect of oxygen saturation in veins and AV difference at baseline on visual acuity change was not statistically significant either ( $p = 0.325$ ,  $p = 0.914$ ).

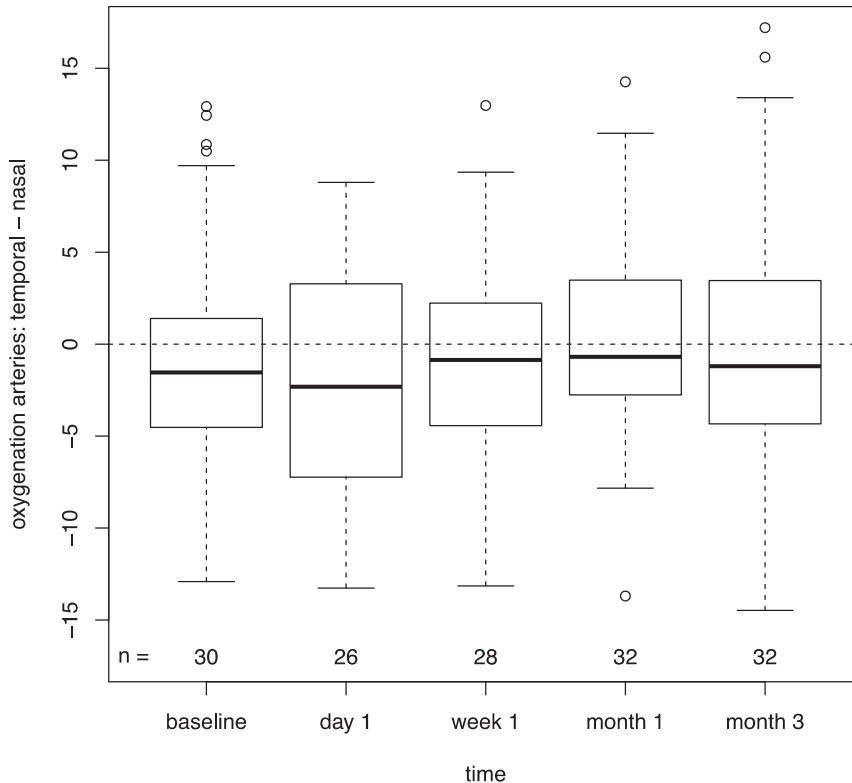
At day 1, mean AV difference (arterio-venous) was significantly lower compared to baseline (estimate [95% CI]:  $-5.3 [-10.32; -0.28]$ ,  $p = 0.039$ ,  $n = 24$ ). At week 1, mean AV was also lower compared to baseline, but the difference was statistically not significant ( $p = 0.33$ ). Hence, the testing procedure stopped; (Table 1, Fig. 6).

**Choroidal volume**

Mean CV of the central mm did not change significantly during the study period (baseline:  $0.20 \text{ mm}^3 \pm 0.04$ , month 3:  $0.20 \text{ mm}^3 \pm 0.04$ , mean difference [95% CI]:  $0.0023 [-0.0053; 0.0098]$ ,  $p = 0.54$  difference baseline versus month 3). There was no statistically significant effect of choroidal volume on functional and morphological outcomes (change in BCVA estimate [95% CI]:  $7 [-76; 90]$ ,  $p = 0.86$ ; change in CRT:  $147 [-577; 871]$ ,  $p = 0.68$ ).

**Vitrectomy plus cataract surgery versus vitrectomy alone**

Comparing visual acuity between patients with same time cataract surgery and without, there was no significant difference between the two groups (ANCOVA: mean difference [95% CI]:  $1.0 [-4.3; 6.4]$ ,  $p = 0.70$  at month 3). For patients without additional cataract surgery, mean CRT was lower compared to baseline for all time points and vice versa for patients with additional cataract surgery (Tables 1 and 2).



**Fig. 4.** Boxplots of the difference of oxygenation of retinal arteries between temporal and nasal area at different time points. The box shows the first quartile (bottom), median (bold line within the box) and the third quartile (top). Outliers are defined as observations that are outside the interval [first quartile  $- 1.5 \times$  interquartile range; third quartile  $+ 1.5 \times$  interquartile range]. Outliers are shown as circles, and in the case of outliers, the whiskers extend to the smallest/largest observation within that interval. If no outliers are present, the whiskers extend to the minimum and the maximum. The sample size ( $n$ ) is shown at the bottom of the graph.

In the cataract surgery group, CRT was higher at month 3 than in the group without ( $441 \pm 51 \mu\text{m}$  versus  $400 \pm 58 \mu\text{m}$  versus; ANCOVA: mean group difference [95% CI]:  $50.6$  [ $14.8$ ;  $86.3$ ],  $p = 0.007$ ).

At month 3, there was no statistically significant difference between groups in the mean change from baseline in oxygenation of retinal arteries or veins (ANCOVA: mean group difference [95% CI]:  $0.114$  [ $6.0$ ;  $6.3$ ]  $p = 0.97$  for arteries;  $3.5$  [ $-4.2$ ;  $11.2$ ],  $p = 0.36$  for veins). Hence, the testing procedure stopped. In the cataract surgery group, baseline values for oxygenation in retinal veins were  $55.7 \pm 11.1$  and in the vitrectomy alone group  $64.4 \pm 13.0$ . In the cataract surgery group, there was an increase in oxygen saturation at day 1 and week one, whereas in the vitrectomy alone group, there was just a slight decrease at these time points.

At day 1, the difference of AV to baseline was lower for the cataract surgery group compared to without, but the difference was not significant

(ANCOVA:  $p = 0.14$ ). [Corrections added on 30 September 2021 after first online publication: new sentence was added: At day 1, the difference of AV to baseline was lower for the cataract surgery group compared to without, but the difference was not significant (ANCOVA:  $p = 0.14$ ).]

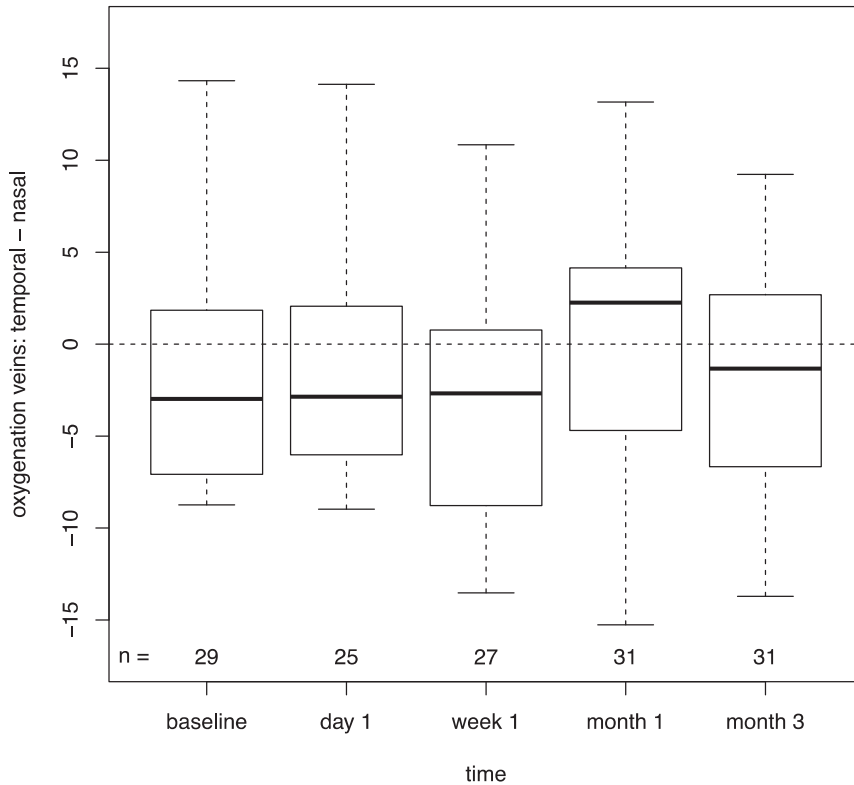
At month 3, no statistically significant difference in the mean change from baseline concerning choroidal volume was found between the groups (ANCOVA, mean group difference [95% CI]:  $0.0089$  [ $-0.0067$ ;  $0.0245$ ],  $p = 0.25$ ).

## Discussion

In the present study, we present the influence of oxygen saturation as well as choroidal volume on postoperative visual and morphological outcomes in eyes with idiopathic ERM. Oxygenation of retinal veins increased significantly starting at month 1, which is in good agreement with a publication of Lim et al., whereas in contrast to

the mentioned study, the arteries merely showed a tendency to increase, but missed the level of significance. In the study of Lim et al. (2014), patients with macular holes and VMT (vitreomacular traction) were included in the analysis. Furthermore, the surgical procedure was combined with phacoemulsification and lens implantation in the bag in all patients. However, comparing the results of combined surgery including cataract surgery with vitrectomy alone in our study, we could not detect significant differences in the oxygenation of arteries.

As mentioned earlier, the oxygen saturation in retinal arteries did not change significantly throughout the whole study period, which is in good agreement with the study of Sin et al. The authors found an increase in retinal vein oxygen saturation using the Oxymap<sup>®</sup> system correspondent to our data (Sín et al. 2014). Increased oxygen tension in retinal venous blood has been described in patients with glaucoma (Olafsdottir et al. 2011; Vandewalle et al. 2014) and patients with diabetes (Hammer et al. 2009; Hardarson & Stefánsson 2012). In patients with glaucoma, a decrease in oxygen consumption is assumed due to atrophy. In diabetic retinopathy, the increase in oxygen tension in retinal veins may be due to an increased velocity due to shunting and obliteration of retinal capillaries. After vitrectomy, it may be assumed that oxygen consumption is lowered due to the removal of the oxygen consuming vitreous, albeit this seems to play a rather minor role (Shui et al. 2009). [Corrections added on 30 September 2021 after first online publication: additional text was added: , albeit this seems to play a rather minor role (Shui et al. 2009).] In a study using MRI, the oxygen saturation in the vitreous cavity was increased after pars plana vitrectomy (Simpson et al. 2013). An increase in oxygenation is one possible mechanism for the improved clinical outcome reported following PPV in diseases associated with retinal ischemia, such as diabetic retinopathy (Tsai et al. 2020), neovascular AMD (Berrelli et al. 2018) and CRVO (Ghashut et al. 2018). Another possible explanation may be an increase in blood velocity due to the mechanical procedure after vitrectomy. However, in our



**Fig. 5.** Boxplots of the difference between the oxygenation of retinal veins in the temporal and nasal area at different time points. The sample size (*n*) is shown at the bottom of the graph.

study, we did not evaluate the oxygen saturation in the vitreous cavity, rather the oxygenation in retinal vessels. Therefore, our data are not directly comparable to the data of those reports.

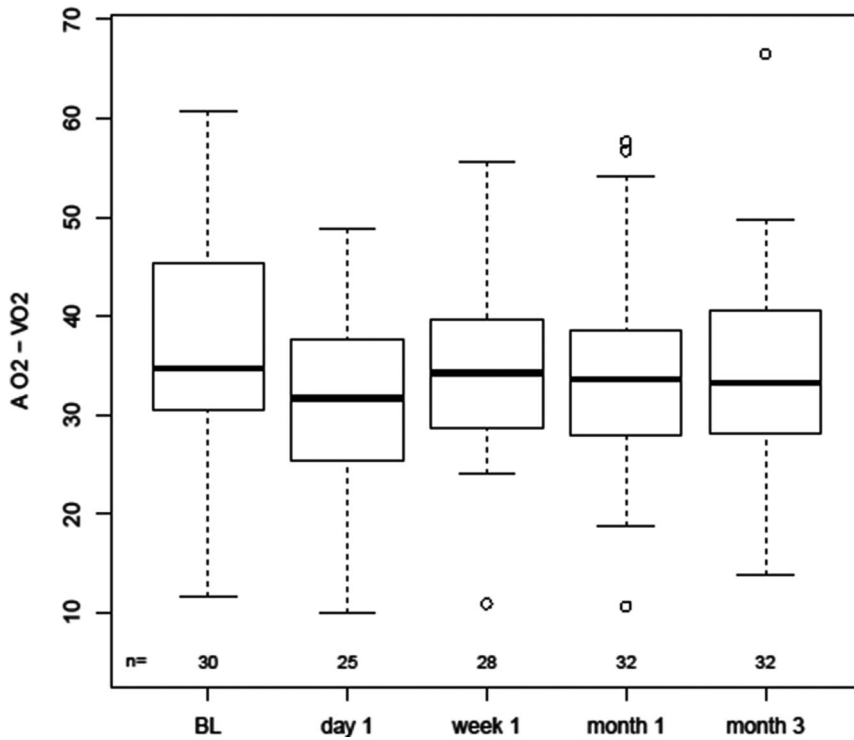
In our study, we analyzed the local difference in oxygen saturation between the nasal and the temporal vessels after the surgical procedure. However, oxygenation of the arteries at day 1 after surgery was slightly lower not reaching the level of significance, maybe due to some local process after vitrectomy and membrane peeling.

There is only little information about correlation of visual acuity and oxygenation of retinal vessels in patients with CRVO (Jeppesen & Bek 2017) and diabetic retinopathy (Bek & Jørgensen 2016), but these data are not comparable because of the different pathophysiology of the diseases. [Corrections added on 30 September 2021 after first online publication: new sentence was added: There is only little information about correlation of visual acuity and oxygenation of retinal vessels in patients with CRVO (Jeppesen

**Table 1.** Mean ± SD (number of valid observations).

	Time	Overall	Without same time cataract surgery	With same time cataract surgery
VA	Baseline	73 ± 11 (28)	71 ± 12 (16)	75 ± 10 (12)
	Week 1	73 ± 9 (31)	71 ± 10 (17)	75 ± 8 (14)
	Month 1	74 ± 8 (32)	73 ± 8 (18)	76 ± 8 (14)
	Month 3	77 ± 7 (32)	76 ± 8 (18)	78 ± 7 (14)
CRT	Baseline	456 ± 84 (32)	469 ± 89 (18)	439 ± 76 (14)
	Day 1	476 ± 56 (28)	494 ± 55 (14)	459 ± 53 (14)
	Week 1	468 ± 55 (31)	468 ± 64 (17)	468 ± 43 (14)
	Month 1	431 ± 54 (32)	421 ± 58 (18)	443 ± 49 (14)
A O <sub>2</sub>	Baseline	97.15 ± 8.31 (30)	97.96 ± 8.31 (17)	96.09 ± 8.52 (13)
	Day 1	94.22 ± 10.09 (25)	94.79 ± 10.62 (13)	93.6 ± 9.91 (12)
	Week 1	98.51 ± 8.75 (28)	97.75 ± 8.69 (14)	99.26 ± 9.07 (14)
	Month 1	98.96 ± 6.4 (32)	99.12 ± 6.2 (18)	98.76 ± 6.88 (14)
V O <sub>2</sub>	Baseline	60.63 ± 12.76 (30)	64.36 ± 12.96 (17)	55.74 ± 11.14 (13)
	Day 1	62.81 ± 11.19 (26)	62.57 ± 7.87 (14)	63.1 ± 14.54 (12)
	Week 1	63.19 ± 11.44 (28)	62.81 ± 8.31 (14)	63.57 ± 14.22 (14)
	Month 1	65.07 ± 9.46 (32)	66.72 ± 7.36 (18)	62.95 ± 11.56 (14)
AV O <sub>2</sub>	Baseline	36 525 ± 11 962 (30)	33 607 ± 10 627 (17)	40 341 ± 12 939 (13)
	Day 1	31 433 ± 9907 (25)	32 295 ± 8044 (13)	30 499 ± 11 905 (12)
	Week 1	35 316 ± 10 079 (28)	34 94 ± 8739 (14)	35 692 ± 11 59 (14)
	Month 1	33 891 ± 10 041 (32)	32 395 ± 7553 (18)	35 813 ± 12 599 (14)
CV	Baseline	0.2026 ± 0.041 (32)	0.1942 ± 0.0364 (18)	0.2134 ± 0.0453 (14)
	Day 1	0.213 ± 0.044 (28)	0.2026 ± 0.0358 (14)	0.2234 ± 0.05 (14)
	Week 1	0.2091 ± 0.0425 (31)	0.1962 ± 0.0387 (17)	0.2248 ± 0.0429 (14)
	Month 1	0.2101 ± 0.0484 (32)	0.193 ± 0.045 (18)	0.232 ± 0.045 (14)
	Month 3	0.2048 ± 0.043 (32)	0.1934 ± 0.0397 (18)	0.2195 ± 0.044 (14)

A O<sub>2</sub> = oxygen saturation in retinal arteries; AV O<sub>2</sub> = arteriovenous difference oxygen saturation; CRT = central retinal thickness (μm); CV = choroidal volume (mm<sup>3</sup>); V O<sub>2</sub> = oxygen saturation in retinal veins; VA = visual acuity (letters ETDRS).



**Fig. 6.** Boxplots of the difference between the oxygenation of retinal arteries and retinal veins at different time points. The sample size (n) is shown at the bottom of the graph.

the retina after vitrectomy. However, in cases with strong microstructural intraretinal alteration, retinal cells may have reduced capacity for oxygen uptake, resulting in higher oxygen saturation in the veins. In a recently published manuscript, the authors stated that parafoveal fractal dimension in the DCP (deep capillary plexus) was significantly correlated with visual acuity before and after ERM surgery and that the parafoveal fractal dimension may serve as a predictive marker for visual outcomes after ERM surgery (Kim & Park 2021) indicating some relationship of microstructural changes and visual acuity. [Corrections added on 30 September 2021 after first online publication: This sentence was corrected to ‘However, in cases with strong microstructural intraretinal alteration, retinal cells may have reduced capacity for oxygen uptake, resulting in higher oxygen saturation in the veins. In a recently published manuscript, the authors stated that parafoveal fractal dimension in the DCP (deep capillary plexus) was significantly correlated with visual acuity before and after ERM surgery and that the parafoveal fractal dimension may serve as a predictive marker for visual outcomes after ERM surgery (Kim & Park 2021) indicating some relationship of microstructural changes and visual acuity.’] A positive, but statistically not significant relationship

& Bek 2017) and diabetic retinopathy (Bek & Jørgensen 2016), but these data are not comparable because of to the different pathophysiology of the diseases.]

A significant negative correlation could be evaluated between oxygenation of retinal veins and visual acuity,

which means, in eyes with lower venous oxygen saturation, the better the visual acuity is expected to be. A possible explanation for this result may be a higher oxygen consumption of the retina after surgery resulting in better visual outcome again supporting the hypothesis of better oxygen supply of

**Table 2.** Mean difference to baseline [95% confidence interval] (number of valid observations).

	Time	Overall	Without same time cataract surgery	With same time cataract surgery
VA	Week 1	1.3 [-1.05, 3.64] (27)	1.07 [-2.18, 4.31] (15)	1.58 [-2.39, 5.56] (12)
	Month 1	2.21 [-0.8, 5.22] (28)	2.31 [-2.02, 6.65] (16)	2.08 [-2.74, 6.9] (12)
	Month 3	4.21 [0.71, 7.72] (28)	4.69 [-0.94, 10.32] (16)	3.58 [-0.81, 7.98] (12)
CRT	Day 1	7.89 [-6.04, 21.83] (28)	-4.14 [-27.51, 19.23] (14)	19.93 [4.3, 35.56] (14)
	Week 1	6.65 [-12.99, 26.28] (31)	-12.12 [-39.93, 15.69] (17)	29.43 [3.66, 55.19] (14)
	Month 1	-25.09 [-49.57, -0.62] (32)	-47.44 [-81.61, -13.28] (18)	3.64 [-29.2, 36.49] (14)
	Month 3	-37.91 [-66.69, -9.12] (32)	-68.61 [-107.05, -30.18] (18)	1.57 [-36.74, 39.88] (14)
A O <sub>2</sub>	Day 1	-2.2 [-4.84, 0.44] (24)	-2.97 [-6.7, 0.76] (13)	-1.29 [-5.67, 3.09] (11)
	Week 1	1.69 [-1.12, 4.5] (26)	-0.53 [-4.96, 3.89] (13)	3.91 [0.26, 7.56] (13)
	Month 1	1.82 [-0.66, 4.31] (30)	1.03 [-2.8, 4.86] (17)	2.86 [-0.52, 6.23] (13)
	Month 3	1.65 [-1.49, 4.8] (30)	1.3 [-2.73, 5.33] (17)	2.12 [-3.58, 7.82] (13)
V O <sub>2</sub>	Day 1	2.89 [-1.46, 7.24] (25)	-1.83 [-7.22, 3.56] (14)	8.89 [2.82, 14.97] (11)
	Week 1	3.76 [-0.8, 8.33] (26)	-2.54 [-9.05, 3.98] (13)	10.06 [5.22, 14.91] (13)
	Month 1	4.72 [0.69, 8.75] (30)	2.33 [-3.41, 8.07] (17)	7.85 [1.9, 13.79] (13)
	Month 3	4.33 [0.3, 8.36] (30)	1.42 [-3.68, 6.51] (17)	8.14 [1.43, 14.85] (13)
CV	Day 1	0.0069 [-0.0029, 0.0167] (28)	0.0038 [-0.0082, 0.0157] (14)	0.0101 [-0.007, 0.0271] (14)
	Week 1	0.0069 [-0.0014, 0.0152] (31)	0.0032 [-0.0085, 0.0149] (17)	0.0114 [-0.0015, 0.0244] (14)
	Month 1	0.0075 [-0.0011, 0.0162] (32)	-0.0011 [-0.0139, 0.0116] (18)	0.0186 [0.009, 0.0283] (14)
	Month 3	0.0023 [-0.0053, 0.0098] (32)	-0.0008 [-0.011, 0.0095] (18)	0.0061 [-0.0061, 0.0183] (14)

A O<sub>2</sub> = oxygen saturation in retinal arteries; CRT = central retinal thickness (μm); CV = choroidal volume (mm<sup>3</sup>); V O<sub>2</sub> = oxygen saturation in retinal veins; VA = visual acuity (letters ETDRS).

between oxygenation of retinal arteries and the change in visual acuity was found in our study. A preoperative analysis of retinal vessel oxygenation may therefore be helpful to guide the decision for surgery. However, this needs to be clarified in further clinical studies.

Choroidal volume as measured in our study did not change significantly during 3 months after surgery and there was no difference if cataract surgery was performed during vitrectomy or not. In a study of Casini et al. choroidal thickness was reduced 6 months after vitrectomy and membrane peeling in the subfoveal, nasal and temporal areas, no difference could be detected if the eye was affected with ERM or not (Casini et al. 2017). Additional cataract surgery showed no influence on choroidal thickness in this study, which is in good agreement to our study. In the aforementioned study, choroidal thickness of the center, 500  $\mu\text{m}$  and 2500  $\mu\text{m}$  around the fovea was measured whereas in our study choroidal volume of the central mm was evaluated, which may be more precise eliminating local changes. Significant diurnal variation of choroidal thickness could be evaluated even in healthy adults with a peak in the morning and a progressive decrease during the day. To minimize this variation, we performed the measurements at the same time in the late morning (Tan et al. 2012).

In eyes with VMT, choroidal thickness was greater than in eyes without, resulting in a reduction of choroidal thickness after vitrectomy just in eyes with VMT, which may be due to anteroposterior traction (Kang et al. 2017). Eyes without VMT showed no change in choroidal thickness up to month 6, which is in good agreement to our study. However, patients with vitreomacular traction were not included in our study.

In another study, choroidal thickness decreased 3 months after vitrectomy and membrane peeling, and there was no difference in thickness between study and fellow eyes, but 50% of the fellow eyes showed ERM, too (Michalewska et al. 2015). However, similar to our results, Li et al showed no significant change in subfoveal choroidal thickness 3 months after vitrectomy and membrane peeling in patients with epiretinal membrane (Li et al. 2019). Hence, we assume that the methods

used for choroidal thickness measurement could be the reason for different outcomes. [Corrections added on 30 September 2021 after first online publication: This sentence was corrected to 'However, similar to our results, Li et al showed no significant change in subfoveal choroidal thickness 3 months after vitrectomy and membrane peeling in patients with epiretinal membrane (Li et al. 2019). Hence, we assume that the methods used for choroidal thickness measurement could be the reason for different outcomes.']

There is a longstanding discussion whether the ILM should be removed, too. Nevertheless, it was shown that ILM peeling might reduce the recurrence of ERM, no difference in visual acuity could be detected between the removal of the ERM alone or the combination with ILM peeling 6 months after surgery (De Novelli et al. 2019). To our knowledge, there is no study showing the influence of ILM peeling on retinal oxygenation or CV. Since the ILM was removed in all patients in our study, we are not able to answer this question with our data.

No difference could be evaluated if cataract surgery was performed additionally in the same procedure as vitrectomy, neither in oxygenation of the vessels nor in choroidal thickness, nor in visual acuity at month 3. However, retinal thickness was significantly higher at month 3 if same time cataract surgery was performed, indicating a prolonged morphological rehabilitation without showing an influence on visual acuity outcomes. Visual acuity increased significantly 3 months after surgery in both groups.

As limitation of our study, the possible influence of the surgery on image quality needs to be mentioned. Therefore, we had to exclude two patients at day 1 after combined surgery from our analysis due to corneal decompensation. At week 1 the image quality in these two patients was good, again. [Corrections added on 30 September 2021 after first online publication: new sentence was added: As limitation of our study, the possible influence of the surgery on image quality needs to be mentioned. Therefore, we had to exclude two patients at day 1 after combined surgery from our analysis due to corneal decompensation. At week 1 the image quality in these two patients was good, again.]

Vitreous surgery has various positive and negative physiological and clinical outcomes. Although vitrectomy can increase the risk of iris neovascularization (Ghartey et al. 1980; Laqua 1980) and often stimulates cataract formation (Holekamp et al. 2005), it may reduce macular edema and the risk of retinal neovascularisation (Blankenship & Machemer 1985) (Hartley et al. 2008; Park & Kim 2010). Vitreous surgery may improve retinal oxygenation and ischemic retinal areas may benefit from the added supply of oxygen. Oxygenation of retinal vessels may even have an influence on visual acuity, perhaps due to reduced or increased oxygen consumption of the retina or a change in blood velocity (Stefánsson 2009). Our study indicated that oxygen saturation may affect the visual acuity outcome but not the CRT in patients after vitrectomy for epiretinal membrane. Choroidal thickness had no statistically significant influence on the study outcomes. [Corrections added on 30 September 2021 after first online publication: This sentence was corrected to 'Our study indicated that oxygen saturation may affect the visual acuity outcome but not the CRT in patients after vitrectomy for epiretinal membrane. Choroidal thickness had no statistically significant influence on the study outcomes.'] However, long-term studies with more participants have to be conducted to further evaluate the exact role of oxygen in the functional outcomes after surgical procedures in the eye.

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