

Retinal Vessel Oxygen Saturation Increases After Vitrectomy

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PURPOSE. To evaluate the effects of vitrectomy on retinal vascular oxygen saturation in an adult population.

METHODS. This was a prospective observational study. Twenty-seven eyes of 27 patients who underwent vitrectomy for macular conditions were included. Retinal oximetry was performed using the Oxymap system prior to vitrectomy and 3 months after surgery and the mean retinal arterial and venous oxygen saturation were measured. The arterial-venous difference (AVD) was calculated as the difference between the arterial and venous saturations. Multivariate linear regression models were constructed to compare oxygen saturation before and after surgery, with adjustments for age, sex, hypertension, hyperlipidemia, diabetes mellitus, and indication for surgery.

RESULTS. The mean age of the subjects was 68.4 ± 8.9 years, 15 (55%) were male and the majority were of Chinese ethnicity (93%). The mean arterial saturation increased significantly after vitrectomy ($101.93 \pm 8.36\%$ vs. $96.16 \pm 14.14\%$, $P = 0.01$). The mean venous saturation also increased significantly after surgery ($59.76 \pm 8.52\%$ vs. $50.40 \pm 11.72\%$, $P = 0.02$). The mean AVD significantly decreased from $45.76 \pm 12.18\%$ before surgery to $42.17 \pm 10.94\%$ after surgery ($P = 0.02$).

CONCLUSIONS. Retinal arterial and venous oxygen saturation are significantly increased after vitrectomy, while the AVD is decreased after vitrectomy.

Keywords: oximetry, vitrectomy, retinal vessel, retinal ischemia

Retinal hypoxia has been hypothesized to play a key role in the development of the complications of diabetic retinopathy (DR).¹⁻¹⁰ Holekamp et al.¹¹ reported that the oxygen tension measured in the vitreous cavity of eyes with DR was lower than that in nondiabetic eyes. Linsenmeier et al.¹² have also shown that the inner retina is hypoxic in diabetic cats. Indirect evidence for the role of retinal oxygenation has also been reported. Drasdo et al.¹³ have reported that retinal oscillatory potentials on electroretinography, a marker of retinal hypoxia, are normalized in diabetic patients with supplemental oxygen administration. Diabetic macular edema has also been shown to improve after breathing pure oxygen.¹⁴

It is currently not possible to measure retinal oxygenation directly in vivo. However, analyzing oxygen saturation within the retinal vessels may give insights into the oxygenation levels in the retina. Hammer and coworkers¹⁵ measured oxygen saturation in the retinal arterioles and venules of 41 diabetic patients with DR severity ranging from mild nonproliferative to proliferative DR, and found that venous oxygen saturation increased with the severity of DR. Similarly, Hardarson and Stefansson¹⁰ found that retinal arteriolar and venular oxygen saturation were both higher in patients with DR than healthy controls. The postulated explanations for these phenomena include capillary occlusion leading to arteriovenous shunting, endothelial dysfunction, and disturbances of retinal vascular autoregulation.

Vitrectomy is frequently employed in the management of the complications of advanced DR including vitreous hemorrhage and tractional retinal detachment.¹⁶⁻¹⁸ However, Stefansson² has postulated that vitrectomy may also be beneficial in DR by improving retinal oxygenation. The removal of the viscous vitreous gel by vitrectomy may help to improve oxygen saturation in the retina by facilitating the diffusion of oxygen from the anterior segment.^{2,6,7}

Data on the effect of vitrectomy on retinal oxygenation are limited. Krepler et al.¹⁹ found that vitrectomy induces significant reductions in ocular blood flow in patients with diabetic retinopathy, suggesting that retinal oxygenation is improved after vitrectomy, while Sin and colleagues²⁰ have shown that oxygen saturation is higher in retinal veins after pars plana vitrectomy. These findings suggest the possibility of increased retinal vascular oxygenation post vitrectomy, with consequent reduction of the risk of DR progression. The aim of this study was to evaluate the effects of vitrectomy on retinal vascular oxygenation in an adult population.

METHODS

This was a prospective observational study. Adult patients undergoing vitrectomy for macular conditions were enrolled consecutively from the vitreoretinal clinics at the Singapore National Eye Centre. The indications for vitrectomy included macular holes (MH), epiretinal membranes (ERM), and vitre-

omacular traction (VMT). Subjects had to have reasonably clear media to allow for fundus imaging.

Detailed interviewer-administered questionnaires were administered to collect relevant sociodemographic data and medical history. Data collected included country and state of birth, marital status, education, occupation and current housing status, participants' lifestyle factors, history of smoking, eye symptoms, use of spectacles, current medications, systemic medical and surgical history, and family history of eye diseases.

All study procedures were performed in accordance with the tenets of the Declaration of Helsinki as revised in 1989. Written informed consent was obtained from the subjects, and the study was approved by the institutional review board of the Singapore Eye Research Institute.

Surgical Procedures

All subjects underwent combined phacoemulsification 23-G vitrectomy surgery with intraocular lens implantation in the bag. The surgical procedures were all performed by the same surgeon (LSL). Regional anesthesia with a peribulbar block was employed in all cases. Phaco-emulsification was performed through a clear corneal incision in all cases. In all cases, posterior vitreous detachment was induced and a thorough vitrectomy with vitreous base shaving was performed. Epiretinal membrane and/or internal limiting membrane peeling was performed as appropriate using MembraneBlue-Dual (DORC, Zuidland, the Netherlands) as a stain. Hexafluoroethane gas was used in nine cases (33.3%) at a nonexpansile 15% concentration. There were no intraoperative or immediate postoperative complications from the surgery.

Retinal Oximetry

Retinal oximetry was performed using the Oxymap system (Oxymap, Inc., Reykjavik, Iceland). The Oxymap system is an automated oximeter that is available as an attachment for the Topcon DX-50 (Topcon, Inc., Tokyo, Japan) fundus camera. The device has been described in detail elsewhere.^{10,20} Briefly, the device consists of a custom made optical adapter with two high-resolution digital cameras (1600 × 1200 square pixels) with 50° fields of view. The device simultaneously acquires two images of the same area of the fundus with two different wavelengths of light. One of the wavelengths (586 nm) is insensitive to oxygen saturation (isobestic), while the other wavelength (605 nm) is sensitive to oxygen saturation (non-isobestic) such that the light absorbance changes with the oxygen saturation. The ratios of the light absorbance have been shown to be linearly related to hemoglobin oxygen saturation. All fundus images were obtained in a darkened room by the same trained technician to minimize operator variability. Fundus images with 50° fields of view centered on the optic disc (OD) were obtained. The device software (Oxymap version 3.1.4; Oxymap, Inc.) generates a color-coded map representing the oxygen saturation in all the imaged vessel segments, with quantitative data on the oxygen saturation (SaO₂) and partial pressure of oxygen (PO₂) generated for each pixel.

Measurements from the images were performed following a standardized protocol (Oxymap protocol for acquisition and analysis of Oxymap T1 oximetry images, version November 2013; Oxymap, Inc.) by a single examiner. In each image, oxygen saturation was measured in all retinal arterioles and venules measuring above 6 pixels in vessel width in the measurement zone which extended from 20 pixels from the (OD) margin (to avoid zones of peripapillary atrophy) to 220 pixels from the OD margin (Fig. 1). Only retinal vessel

segments with a minimum length of 100 pixels were included. For branching vessels, the parent branch was measured. If the parent branch was less than 100 pixels in length, daughter branches were also measured. At vessel crossings, the distal segment was chosen unless this segment was less than 100 pixels in length, in which case the proximal segment was measured. The localization by quadrant for each vessel segment was assigned according to the end point of the vessel. The examiner was masked to all clinical details both pre and post vitrectomy.

Overall quadrant retinal oxygen saturation level was calculated as the sum of each retinal oxygen saturation measurement multiplied by the diameter of each vessel in the fourth power, further divided by the sum of diameter of each vessel in the fourth power.^{21,22}

Mean oxygen saturation

$$= \frac{S_1 \cdot d_1^4 + S_2 \cdot d_2^4 + S_3 \cdot d_3^4 + S_4 \cdot d_4^4 + S_5 \cdot d_5^4 + S_6 \cdot d_6^4 + S_7 \cdot d_7^4 + S_8 \cdot d_8^4}{d_1^4 + d_2^4 + d_3^4 + d_4^4 + d_5^4 + d_6^4 + d_7^4 + d_8^4} \quad (1)$$

S_n = saturation of n vessel segment
 d = diametes of n vessel segment

The arteriolar-venular diameter (AVD) was calculated as the difference between retinal arteriolar oxygen saturation and retinal venular oxygen saturation.²²

All subjects underwent baseline imaging from 2 weeks before until 24 hours before the time of surgery. Postoperative imaging was repeated at approximately 3 months after surgery to allow for restoration of corneal/media clarity after surgery.

Statistical Analysis

Multivariate linear regression models were constructed with the postsurgery measurement as the dependent variable and the presurgery measurement as the explanatory variable, with adjustments for age, sex, hypertension, hyperlipidemia, diabetes mellitus, and indication for surgery. We regarded P values of less than 0.05 from two-sided tests as statistically significant. All statistical analyses were performed using SPSS version 16.0 (SPSS, Inc., Chicago, IL, USA).

RESULTS

We recruited 27 patients in total. The mean age of the subjects was 68.4 ± 8.9 years, 15 (55%) were male and the majority were of Chinese ethnicity (93%). The baseline characteristics, stratified by sex, are presented in Table 1. There were no significant sex differences in age, race, diabetes mellitus, hypertension, hyperlipidemia, or indication for surgery. The commonest indication for surgery was ERM (59%), followed by MH (33%), and VMT (7%).

The mean arterial saturation was $96.16 \pm 14.14\%$ before surgery and $101.93 \pm 8.36\%$ after surgery. The mean venous saturation was $50.40 \pm 11.72\%$ before surgery and $59.76 \pm 8.52\%$ after surgery. The mean AVD was $45.76 \pm 12.18\%$ before and $42.17 \pm 10.94\%$ after surgery. In unadjusted analyses, the mean arterial saturation and venous saturation were significantly greater after surgery than before ($P = 0.01$ and $P < 0.001$, respectively), while the mean AVD was not significantly different after surgery ($P = 0.11$). In multivariate analyses adjusting for age, sex, hypertension, hyperlipidemia, diabetes mellitus, and indication for surgery, the mean arterial saturation and venous saturation were still significantly greater after surgery than before ($P = 0.001$ and $P = 0.02$, respectively),

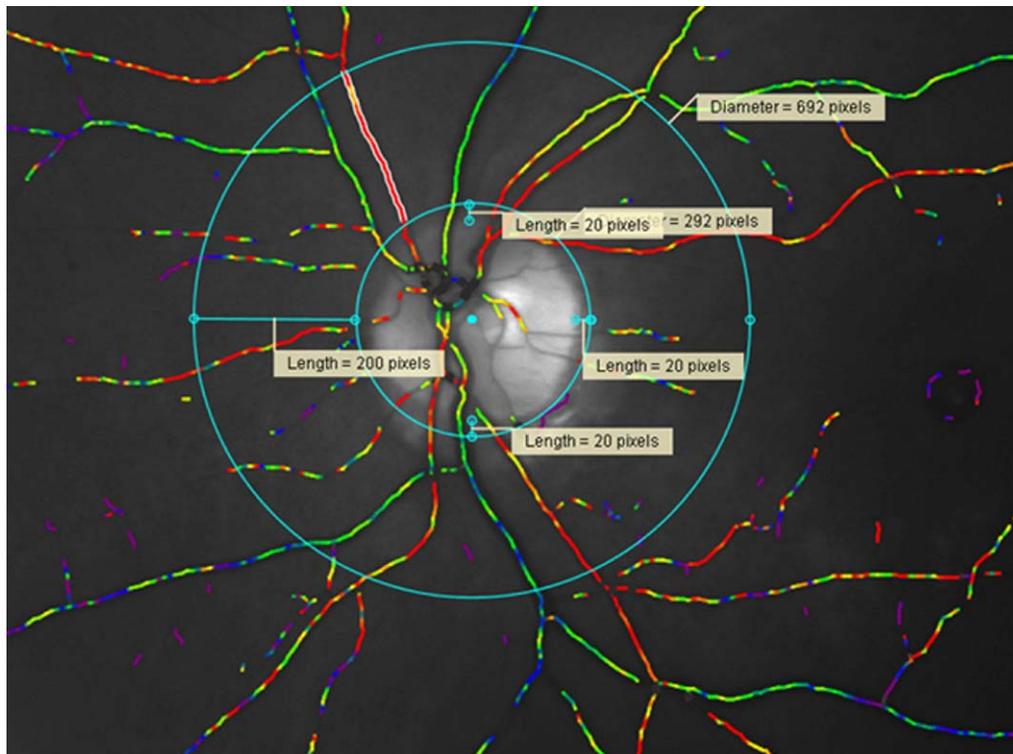


FIGURE 1. Sample Oxymap image analysis. The arteriolar and venular saturations within the measurement zone (bounded by the two circles) were measured. In this image, the superonasal arteriole has been selected for analysis.

while the mean AVD was significantly smaller after surgery than before ($P = 0.002$; Table 2).

Representative images from a patient taken before and after vitrectomy are shown in Figure 2.

DISCUSSION

In this cohort of adult patients undergoing vitrectomy for various macular indications, we have shown that retinal arteriolar oxygen saturation and retinal venular oxygen saturation as measured by the Oxymap system are significantly altered after surgery. Both retinal arteriolar oxygen saturation and retinal venular oxygen saturation increased after vitrectomy surgery.

Data on the effects of vitrectomy on the retinal circulation are relatively limited. There is only one published study

evaluating changes in retinal vessel oxygenation after vitrectomy. Sin et al.²⁰ evaluated changes in retinal oxygenation in 20 subjects undergoing vitrectomy for MH or ERM. Subjects were imaged before and 1.5 months after surgery (mean 45 days). Vitrectomy was found to increase retinal venous saturation but not arterial saturation. Our findings that retinal venous saturation increased are consistent with their findings, but, in contrast, we also found increased arterial saturation. Arterial-venous difference was not analyzed in their study. There are notable differences in our studies that may account for the disparities. The vessel analyses by Sin et al.²⁰ were conducted on only one vessel segment (lower temporal branch or upper temporal branch) rather than on all four quadrants. We believe that analyzing and averaging all four quadrants improves the reliability of measurements, and is also more representative of global retinal vascular oxygenation. In a separate study from our center (paper under review), the method of analysis we used was shown to have good intragrader (intraclass correlation coefficient [ICC] 0.93–0.98), intergrader (ICC 0.76–0.98), and intravisit (ICC 0.76–0.91) repeatability. All of our subjects underwent combined phacoemulsification-vitrectomy surgery. As such, variability in image quality due to media opacity was also reduced.

Most other studies evaluating the effects of vitrectomy on the retinal circulation have focused on retinal blood flow and blood flow velocity. Yagi and coworkers²³ evaluated blood flow velocity in the perifoveal capillaries before and after vitrectomy for ERM and found that perifoveal blood flow increased after surgery. Similarly, Kadonosono et al.²⁴ has also shown increased perifoveal capillary blood flow velocity after vitrectomy for ERM. In subjects undergoing vitrectomy for diabetic complications; however, conflicting results have been obtained. Sugiyama and Ando²⁵ compared the effects of vitrectomy, laser photocoagulation, and observation on capillary perfusion in the temporal raphe area and found that

TABLE 1. Distribution of Baseline Characteristics by Sex

	Male, n = 15	Female, n = 12	P Value
Age, y	67.5 ± 10.1	69.5 ± 7.4	0.58
Race			
Chinese	14	11	
Malay	1	1	0.87
Diabetes mellitus (number, %)	4 (27%)	4 (33%)	0.52
Hypertension (number, %)	10 (67%)	9 (75%)	0.48
Hyperlipidemia (number, %)	11 (73%)	9 (75%)	0.64
Indication for surgery			
MH	4	5	
ERM	11	5	
VMT	0	2	0.13

TABLE 2. Mean Retinal Vessel Saturation and Arterial-Venous Saturation Difference Before and After Vitrectomy

	Previtrectomy, %	Postvitrectomy, %	P Value*
Arterial saturation	96.16 ± 14.14	101.93 ± 8.36	0.001
Venous saturation	50.40 ± 11.72	59.76 ± 8.52	0.02
Arterial-venous difference	45.76 ± 12.18	42.17 ± 10.94	0.002

* Adjusted for age, sex, hypertension, hyperlipidemia, diabetes mellitus, and indication for surgery.

vitrectomy had the greatest effect on increasing perfusion. Kadonosono et al.²⁶ has also shown increased perifoveal capillary blood flow velocity after vitrectomy for diabetic macular edema. However, Park et al.²⁷ measured macular blood flow using a Heidelberg Retinal Flowmeter in subjects undergoing vitrectomy for diffuse diabetic macular edema and found that mean macular blood flow at 12 weeks after vitrectomy was significantly lower than preoperative blood flow. These changes were correlated with reduction in macular edema. Krepler et al.¹⁹ evaluated changes in ocular blood flow after vitrectomy for various diabetic complications and found reductions in pulsatile choroidal blood flow as well as mean blood flow velocity in the central retinal artery and the posterior ciliary arteries. The effects of diabetic vitrectomy on retrobulbar hemodynamics have also been evaluated. Sullu et al.²⁸ has shown improvements in ophthalmic artery and central retinal artery blood flow velocity after vitrectomy with reduced resistance to blood flow in the central retinal artery. Changes in retinal blood flow may help to explain our findings. Increased central retinal artery flow could directly lead to increase retinal arteriolar saturation. Although the AVD was possibly lower after surgery, this was only demonstrated after multivariate adjustment, and may thus be less certain. Faster arterial-venous transit through the capillary bed would imply reduced oxygen extraction by the retinal tissues and correspondingly higher retinal venous saturation. Hammer et al.¹⁵ has measured oxygen saturation in the retinal arterioles and venules of diabetic patients with DR severity ranging from mild nonproliferative to proliferative DR and found that venous oxygen saturation increased with the severity of DR. Similarly, Hardarson and Stefansson¹⁰ found that retinal arteriolar and venular oxygen saturation were both higher in patients with DR than healthy controls. These phenomena may similarly

reflect arteriovenous shunting and reduced oxygen extraction by the capillary bed.

Vitrectomy is frequently employed in the management of the complications of advanced DR, including vitreous hemorrhage and tractional retinal detachment.¹⁶⁻¹⁸ The relationship between the vitreous and retinal metabolism is complex. However, Stefansson^{2,3} has postulated that vitrectomy may also be beneficial in DR by improving retinal oxygenation. The removal of the viscous vitreous gel by vitrectomy may help to improve oxygen saturation in the retina by allowing for diffusion or bulk transport of oxygen from the anterior segment.^{2,6,7} At this point, we are unable to conclude if the increased retinal arterial and venular oxygen saturation induced by vitrectomy is directly beneficial in diabetic retinopathy. It is also an unfortunate limitation of the Oxymap system that clear media are required for retinal vessel imaging, precluding the possibility of conducting a study to evaluate changes in retinal vessel oxygenation after vitrectomy for proliferative DR with vitreous hemorrhage. Vitrectomy has also been employed in the management of the complications of retinal vein occlusion (RVO). Vitrectomy has been evaluated for the treatment of cystoid macular edema in branch RVO and shown to reduce macular edema and improve visual acuity.²⁹ Other, more controversial surgical procedures like radial optic neurotomy and arteriovenous sheathotomy have had less success in improving ocular perfusion and clinical outcomes, and it is possible that it is the removal of the vitreous rather than these additional surgical manipulations that benefits the patient.³⁰⁻³²

The strengths of our study include a relatively large cohort of subject undergoing surgery, as well as the standardized assessments of Oxymap system parameters as well as systemic covariates. As discussed earlier, our method of analysis has good reliability and repeatability. Furthermore, our examiner

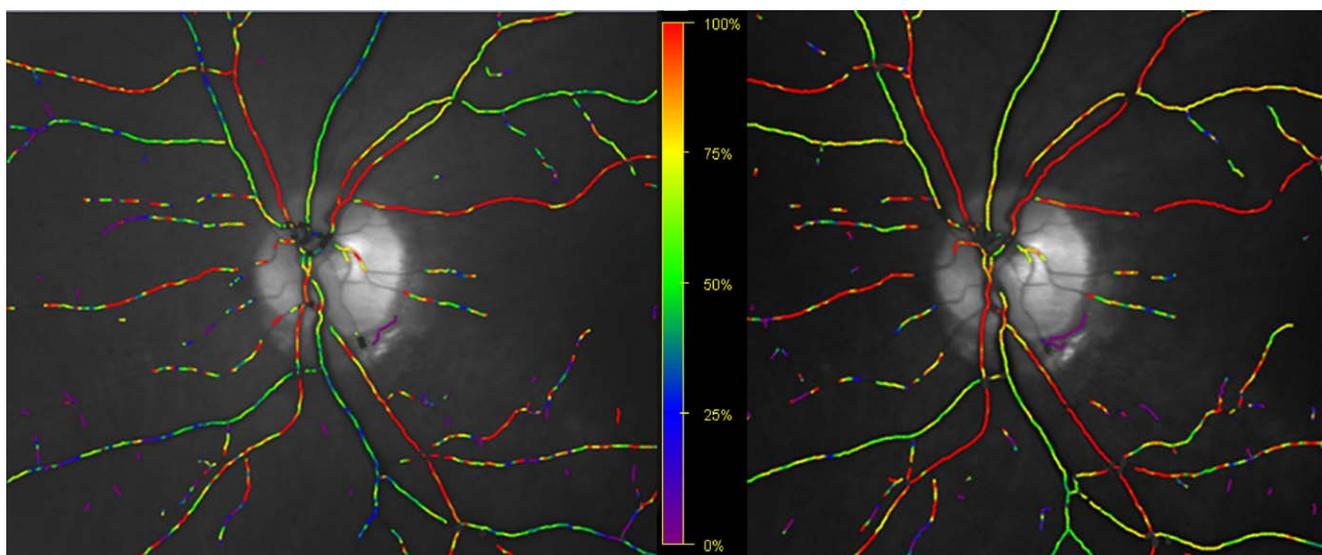


FIGURE 2. Sample images taken from the same eye before (*left*) and after (*right*) vitrectomy.

was blinded to the pre- or postoperative status of the eyes at the time of image analysis. General limitations of our study include the possibility of selection bias, and the cross-sectional design, which restricts inferences of causality. All of our subjects underwent combined phacoemulsification-vitrectomy surgery, and it is possible that cataract extraction itself may have influenced the results. The Oxymap system readings may be susceptible to changes in the cardiac cycle. We also measured arterial saturation values of over 100%, which has been known to occur due to the challenging nature of calibrating retinal oximeters.^{10,33} The Oxymap system is a form of two wavelength oximetry that uses calibration coefficients derived from oxygen saturation values measured in predominantly Caucasian subjects.³⁴ Our population was racially homogenous with all subjects of Asian ethnicity and 93% of Chinese descent, and it is possible that cutaneous and fundus pigmentation could have contributed to skewed absolute saturation readings. As the relationship between the optical density ratio and the eventual calculated oxygen saturation value is linear, this would not have affected the comparisons we made.³³ Lastly, It is important to note that the Oxymap system and all other oximeters produce oximetry that is only an estimate of the true oxygen saturation.

In conclusion, retinal arterial and venous oxygen saturation increase after vitrectomy. Our results suggest that vitrectomy has measurable effects on ocular hemodynamics and retinal oxygenation. Further study is warranted to define the clinical role of the Oxymap system, particularly in the context of microvascular diseases of the retina, such as diabetes mellitus.

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