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Retina

Colorimetric Analyses of the Optic Nerve Head and Retina Indicate Increased Blood Flow After Vitrectomy

Onur İnam[1,2], Ayman El-Baz[3], Henry J. Kaplan[4,5], and Tongalp H. Tezel[1,4]

[1] Department of Ophthalmology, Edward S. Harkness Eye Institute, Vagelos College of Physicians and Surgeons, Columbia University Irving Medical Center, New York, NY, USA
[2] Department of Biophysics, Faculty of Medicine, Gazi University, Ankara, Turkey
[3] Bioengineering Department, University of Louisville, Louisville, KY, USA
[4] Department of Ophthalmology & Visual Sciences, Kentucky Lions Eye Center, University of Louisville School of Medicine, Louisville, KY, USA
[5] Department of Ophthalmology, Saint Louis University, School of Medicine, St. Louis, MO, USA

Correspondence: Tongalp H. Tezel, Department of Ophthalmology, Edward S. Harkness Eye Institute, Vagelos College of Physicians and Surgeons, Columbia University Irving Medical Center, 622 West 168th Street, 18th Floor, Suite 18201B, Mail Box 200, New York, NY 10032, USA.
e-mail: tht2115@cumc.columbia.edu

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Purpose: The purpose of this study was to evaluate the impact of vitrectomy and posterior hyaloid (PH) peeling on color alteration of optic nerve head (ONH) and retina as a surrogate biomarker of induced perfusion changes.

Methods: Masked morphometric and colorimetric analyses were conducted on preoperative (<1 month) and postoperative (<18 months) color fundus photographs of 54 patients undergoing vitrectomy, either with (44) or without (10) PH peeling and 31 years of age and gender-matched control eyes. Images were calibrated according to the hue and saturation values of the parapapillary venous blood column. Chromatic spectra of the retinal pigment epithelium and choroid were subtracted to avoid color aberrations. Red, green, and blue (RGB) bit values over the ONH and retina were plotted within the constructed RGB color space to analyze vitrectomy-induced color shift. Vitrectomy-induced parapapillary vein caliber changes were also computed morphometrically.

Results: A significant post-vitrectomy red hue shift was noted on the ONH (37.1 degrees $\pm$ 10.9 degrees vs. 4.1 degrees $\pm$ 17.7 degrees, $P < 0.001$), which indicates a 2.8-fold increase in blood perfusion compared to control (2.6 $\pm$ 1.9 vs. 0.9 $\pm$ 1.8, $P < 0.001$). A significant post-vitrectomy increase in the retinal vein diameter was also noticed (6.8 $\pm$ 6.4% vs. 0.1 $\pm$ 0.3%, $P < 0.001$), which was more pronounced with PH peeling (7.9 $\pm$ 6.6% vs. 3.1 $\pm$ 4.2%, $P = 0.002$).

Conclusions: Vitrectomy and PH peeling increase ONH and retinal blood flow. Colorimetric and morphometric analyses offer valuable insights for future artificial intelligence and deep learning applications in this field.

Translational Relevance: The methodology described herein can easily be applied in different clinical settings and may enlighten the beneficial effects of vitrectomy in several retinal vascular diseases.

Introduction

Impaired hemodynamics affecting optic nerve head (ONH) and retinal perfusion constitutes a primary pathological process in various sight-threatening conditions, including diabetic retinopathy, papillopathy, retinal vein occlusions, retinopathy of prematurity, and non-arteritic anterior ischemic optic neuropathy.[1–8] Furthermore, disrupted vascular supply significantly contributes to the pathogenesis of several notable pathologies, such as glaucoma and hereditary retinal degenerations.[9–11] These abnormalities can lead to capillary dropout, angiogenesis, and tissue hypoxia, ultimately affecting retinal and ONH perfusion.[12] Often, ONH and retinal perfusion impairment may remain occult and act as an underlying risk factor for major vascular events. For instance, a study utilizing

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optical coherence tomography angiography (OCTA) discovered lower peripapillary vessel and perfusion densities in the fellow eyes of patients with unilateral retinal vein occlusion compared to those in healthy control subjects.[6] Thus, apart from a local effect that leads to retinal vein occlusion in one eye, there is underlying impaired blood perfusion involving both eyes in these patients. Epidemiological studies point out that systemic hypertension, atherosclerosis, and diabetes are the main pathologies leading to occult perfusion defects in the retina.[13,14]

Several studies indicate a higher rate of involvement of the retinal vasculature compared with vascular beds during systemic vascular diseases. For example, clinical signs of retinal vessel involvement precede and can be a predictor for clinical participation of kidney vasculature[15,16] in diabetes, and retinal veins suffer from thromboembolic events 420 times more than cerebral vessels.[17,18] The higher vulnerability of retinal vasculature indicates a role of local factors on the retinal and ONH blood flood.

The role of mechanical forces exerted by vitreoretinal solid attachments on the disruption of blood flow was suggested in clinical studies.[19,20] In the case of retinal vein obstruction, vitrectomy and posterior hyaloid peeling have been shown to restore blood flow in an occluded retinal vein by relieving traction.[21–23] Similarly, vitrectomy in diabetic retinopathy restores the perifoveolar perfusion,[20] and improves retinal venous oxygenation in macular holes and puckers by increasing the retinal blood flow.[24]

Retinal perfusion changes have classically been assessed by either observing changes in clinical features, that is, the disappearance of macular edema, or by estimating the ocular blood flow rate with color Doppler imaging,[25] assessing tissue oxygenation with retinal oximetry,[26] and imaging ocular vascular structure with OCTA[27] or fluorescein fundus angiogram. However, most of these studies extract information from retinal macrovessels, which do not reflect the perfusion in the retinal microvascular bed. In addition, these techniques require costly instruments, a limited field of view, and possible artifacts that can interfere with the accuracy and reliability of assessments and fail to show the whole tissue perfusion.

Herein, we aimed to test the impact of vitrectomy and posterior hyaloid removal on ONH and retinal perfusion. We used a novel mathematical method based on colorimetric and morphometric analysis of the ONH and retinal vasculature using pre- and postoperative color fundus photographs. The inspiration for these analyses was our intraoperative observation of retinal vessel engorgement and red color shift of the ONH as soon as we peeled the posterior hyaloid, all indicating improved perfusion.

Materials and Methods

This study is a retrospective case-control study approved and monitored by the Institutional Review Board of the University of Louisville's School of Medicine and conducted per the ethical standards outlined in the Declaration of Helsinki for research activities.

Study Groups and Inclusion Criteria

The study includes two surgical groups and an age- and gender-matched control group. The surgery groups underwent vitrectomy and were further divided into two subgroups: those with posterior hyaloid peeled (PHP(+)) and those without (PHP(−)). Subjects in the experimental group were selected from patients who had undergone vitrectomy for conditions such as diabetic retinopathy, vitreomacular traction, or a macular hole. Data for the control group were obtained from unoperated patients with diabetic retinopathy, macular pucker, vitreal opacities, or patients who presented for refractive eye examinations who served as a baseline for temporal variations in retinal vessel diameter and colorimetric parameters. Attention was paid to match the systemic co-morbidities, that is, diabetes, hypertension, hyperlipidemia, obstructive sleep apnea, and cardiac morbidities among experimental and control groups. Patients with high myopia, significant lenticular or visual axis opacities, and reported postoperative complications, such as intraocular hemorrhage, were excluded from the study. All relevant information, such as age, gender, visual acuity, intraocular pressure (IOP), preoperative and postoperative fundus photograph time lapses, and surgical history of the patients were gathered and standardized from conventional and digital archives.

Colorimetric and Morphometric Analyses Optic Nerve Head and Retina

Morphometric and colorimetric analyses were conducted on preoperative (<1 month) and postoperative (<18 months) fundus photographs of patients who had undergone vitrectomy, as well as on the control group within the same time intervals, all in a masked fashion. The 24-bit red, green, and blue (RGB) coded-color fundus images were obtained using a

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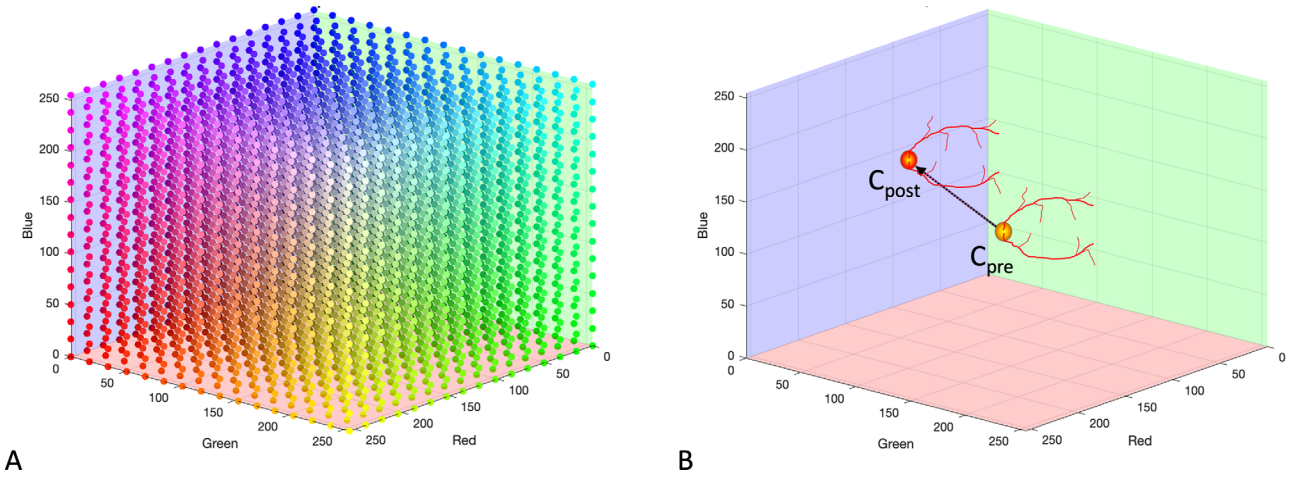


Figure 1. (**A**) The RGB color space diagram shows three axes representing the red, green, and blue scales. *Dots* on the diagram represent possible color combinations within this Cartesian coordinate system, which can be as high as 256^3 combinations. (**B**) C_{pre} demonstrates the preoperative color value, and C_{post} demonstrates the postoperative color value within the RGB color space. The *arrow* indicates the shift in color postoperatively. The directional change of the vector was calculated from the RGB values of two points.

non-mydriatic fundus camera (Topcon TRC-NW8; Topcon Corporation, Tokyo, Japan). The hue and saturation of the parapapillary venous blood column and macula were calculated and utilized to calibrate the corresponding 24-bit images. The foveal retinal pigment epithelium and choroid chromatic spectra were subtracted to minimize color aberrations. Bit values for the red (R), green (G), and blue (B) channels (ImageJ, National Institutes of Health [NIH])[28] over the ONH and retina were plotted within the RGB color space (Fig. 1) to assess the color shift induced by vitrectomy and the fold difference in blood perfusion. RGB color space is a cartesian system in which axes were red, green, and blue values are plotted on the X, Y, and Z axes (see Fig. 1A). Each color is assigned an 8-bit value between 0 and 255. A numerical value can be assigned to more than 16 million colors (24-bit RGB = $2^8 \times 2^8 \times 2^8$ = 16.7 million). This allows the calculation of color changes as a vectorial shift between preoperative and postoperative values, as is seen in Figure 1B. RGB color space has been used for image analyses in different disciplines[29,30] and retinal image analyses[31,32] because of its reliability and simplicity.

Another key measure was the variation in retinal vessel diameter before and after vitrectomy. Morphometric analysis of changes in the diameter of parapapillary veins was performed using pre- and postoperative measurements. Calipers were used to measure color fundus photographs for determining the blood vessel diameter pre- and postoperatively in all patients, and the ratio of this change in diameter was recorded for superior temporal (ST), inferior temporal (IT), and average of both (ST + IT).

Calculations

Two corrections were made to the raw RGB values of the ONH and retina. Initially, the RGB bit value of the parapapillary venous blood column was extracted from the ONH and retinal color spectra to eliminate any hue and saturation artifacts. In addition, the color values of 5 areas within the macula, each 0.5 × 0.5 mm in size, were selected from the preoperative fundus images to determine the color spectra of the RPE and choroid. These values were used to eliminate the confounding effects of the choroidal and RPE pigment on calculations. Attention was paid not to include the visible retinal arterioles and venules within the frame while selecting the images for this purpose. Correcting the ONH and retinal images, RGB values resulted in adjusted values of the images in RGB bits. Pre and postoperative RGB bit values were then plotted on a Cartesian coordinate system constructed within a 3-dimensional RGB environment, as described before.[33] Plotting the RGB values on the color space yielded a vectorial representation of the preoperative and postoperative color values (see Fig. 1). The center of the 3D color space environment (point $X_0Y_0Z_0$) represents black color, and each axis had 256 saturation levels (see Fig. 1). The vectorial shift induced by vitrectomy was calculated using the following formula:

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$$Direction\ of\ the\ Color\ Vector\ Change = Postoperative\ CSV - Preoperative\ CSV$$

$$Direction\ of\ the\ Color\ Vector\ Change = \left[\tan^{-1}\left[\frac{[R_{Post} - [[\sin(30 * \frac{\pi}{180})] * (G_{Post} + B_{Post})]]}{[[\cos(30 * \frac{\pi}{180})] * (G_{Post} - B_{Post})]}\right]\right] - \left[\tan^{-1}\left[\frac{[R_{Pre} - [[\sin(30 * \frac{\pi}{180})] * (G_{Pre} + B_{Pre})]]}{[[\cos(30 * \frac{\pi}{180})] * (G_{Pre} - B_{Pre})]}\right]\right]$$

Pre: preoperative; Post: postoperative; R: red; b: Blue; g: Green; CSV: color spectrum value.

The equivalent blood flow changes required to create the same color axis shift were calculated similarly to estimating optic nerve perfusion changes based on color value changes.[34,35] For this purpose, the following formula was used:

$$Equivalent\ Blood\ Flow\ Change = \frac{\left[R_{Pre} - [0.5 * (G_{Pre} + B_{Pre})] - \left[[\tan[CSV_{Post} * (\frac{\pi}{180})]] * \left(\frac{\sqrt{3}}{2}\right) * |G_{Pre} - B_{Pre}|\right]\right]}{\left[\left[[\tan[CSV_{Post} * (\frac{\pi}{180})]] * \left(\frac{\sqrt{3}}{2}\right) * (G_V - B_V)\right] + [0.5 * (G_V + B_V)] - R_V\right]}$$

Pre: preoperative; Post: postoperative; R: red; B: blue; G: green; CSV: color spectrum value; V: parapapillary vein.

Statistical Evaluation

Data were collected and presented as mean ± standard deviation, 95% upper and lower limits of the confidence interval for continuous variables, and percentages and numbers for categorical variables. The normality of the data was assessed using the Shapiro-Wilk Normality test. Student's *t*-test was used for normally distributed variables, whereas the Mann-Whitney *U* test was employed for variables not normally distributed. A *P* value of < 0.05 was considered to indicate a statistically significant difference. All analyses were conducted using various statistical software programs (SigmaStat; SPSS Inc, Chicago, IL, USA; IBM SPSS V28.0, Armonk, NY, USA: IBM Corp; MATLAB version: R2023b; Natick, Massachusetts: The MathWorks Inc.).

Results

The cohort consisted of 54 eyes that underwent vitrectomy, 44 of which had posterior hyaloid peeling and 10 without, along with 31 non-vitrectomized control eyes. There were no significant differences in average patient age (63 ± 17 vs. 65 ± 12), gender distribution, or the time interval between two fundus photographs (8 ± 11 vs. 8 ± 7 months) between the surgical and control groups ($P > 0.05$).

Colorimetric Analyses of the ONH

Table 1 provides the mean, standard deviation, and confidence interval values for the direction of color vector change and the equivalent blood flow change in the ONH. The surgical group showed significantly higher values in both the direction of color vector change (37.06 ± 10.94 vs. 4.12 ± 17.65, $P < 0.001$) and equivalent blood flow change (2.58 ± 1.94 vs. 0.94 ± 1.78, $P < 0.001$) compared to the control group. Similarly, both the PHP(+) group (direction of color vector change = 36.70 ± 10.85 vs. 4.12 ± 17.65, $P < 0.001$; equivalent blood flow change = 2.44 ± 1.84 vs. 0.94 ± 1.78, $P < 0.001$); and the PHP(−) group (direction of color vector change = 38.63 ± 11.81 vs. 4.12 ± 17.65, $P < 0.001$; equivalent blood flow change = 3.19 ± 2.33 vs. 0.94 ± 1.78, $P = 0.001$) exhibited significantly higher values than the control group (see Table 1, Fig. 2).

Table 1. Optic Nerve Head Metrics

Metric	Group	Mean	Std	95% CI Lower	95% CI Upper
Direction of the color vector change	PHP(+)	36.70	10.85	33.40	40.00
	PHP(−)	38.63	11.81	30.18	47.08
	Surgical	37.06	10.94	34.07	40.04
	Control	4.12	17.65	−2.35	10.60
Equivalent blood flow change	PHP(+)	2.44	1.84	1.88	3.01
	PHP(−)	3.19	2.33	1.52	4.86
	Surgical	2.58	1.94	2.05	3.12
	Control	0.94	1.78	0.29	1.59

PHP(+) $N = 44$, PHP(−) $N = 10$, Control $N = 31$, PHP(+): posterior hyaloid peeling group, PHP(−): posterior hyaloid non-peeling group, Std: standard deviation, CI: confidence interval.

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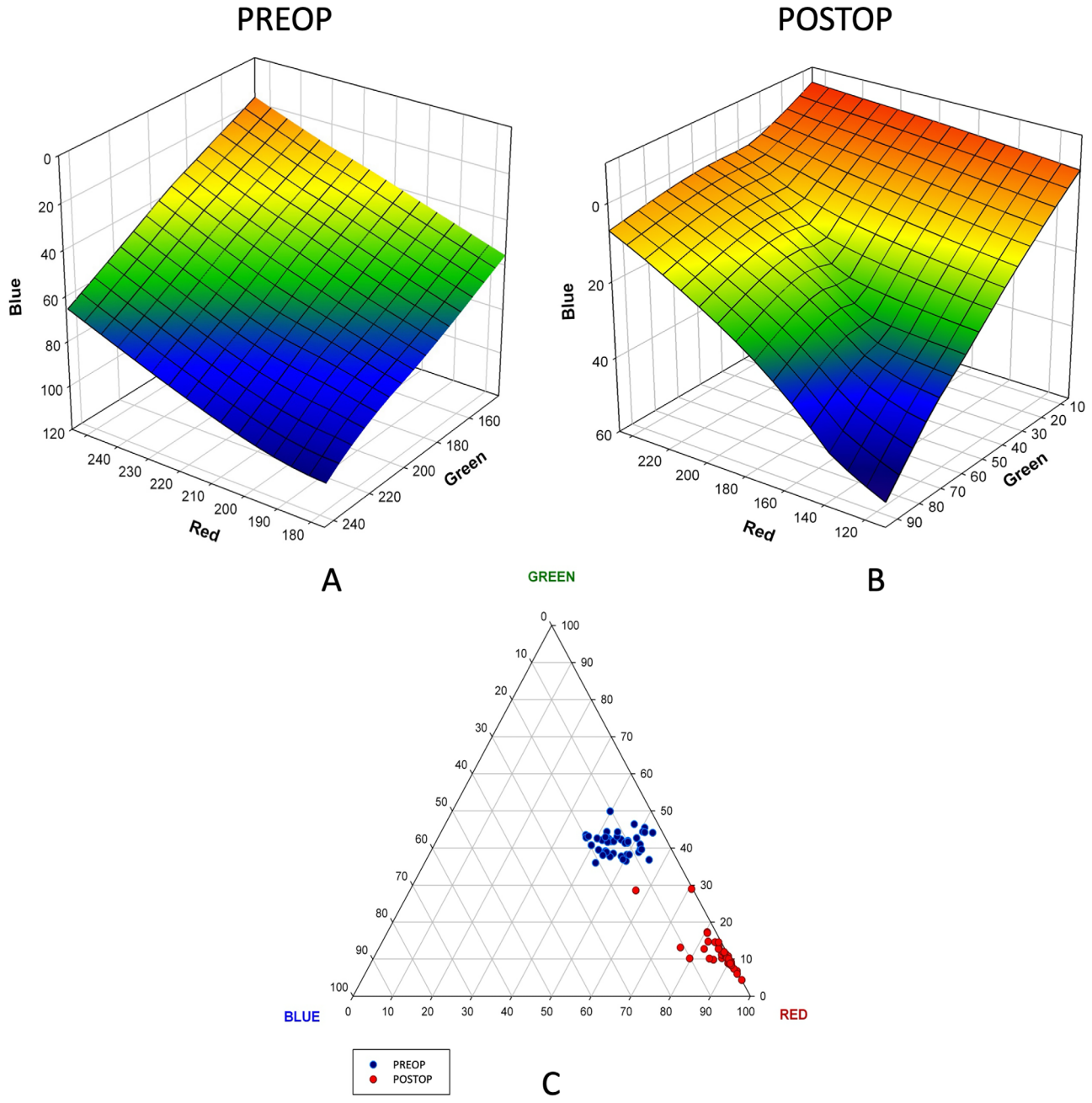


Figure 2. (**A**) Preoperative and (**B**) postoperative surface plots for RGB values of the optic nerve head. Preoperative and postoperative RGB values of patients who underwent vitrectomy were plotted on the 3D mesh. The smoothened surface plot changes after vitrectomy demonstrate a shift toward the red color due to increased optic nerve perfusion. (**C**) Preoperative and Postoperative color shift in a color triangle. Each red, green, and blue intensity was transformed into a scale of 1 to 100, and each point represents an RGB value in a triangular coordinate framework. The *blue points* denote preoperative values, whereas the *red points* represent postoperative values. Change in ONH blood perfusion after vitrectomy in the surgical group can be seen. PREOP: preoperative; POSTOP: postoperative.

Colorimetric Analyses of the Retina

Table 2 presents retinal metrics for different groups. For the direction of color vector change, the surgical group did not significantly differ from the control group (15.79 ± 24.22 vs. 5.28 ± 7.99, $P = 0.069$). In contrast, the PHP(+) group exhibited a higher value compared to the control group (15.26 ± 21.81 vs. 5.28 ± 7.99, $P = 0.013$), whereas the PHP(−) group showed no significant difference (17.27 ± 31.33 vs. 5.28 ± 7.99, $P = 0.724$).

Similarly, for equivalent blood flow change, the surgical group's values were not significantly different than those of the control group (1.96 ± 2.29 vs.

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Table 2. Retina Metrics

Metric	Group	Mean	Std	95% CI Lower	95% CI Upper
Direction of the color vector change	PHP(+)	15.26	21.81	6.80	23.71
	PHP(−)	17.27	31.33	−5.14	39.68
	Surgical	15.79	24.22	7.83	23.75
	Control	5.28	7.99	2.30	8.27
Equivalent blood flow change	PHP(+)	2.22	2.35	1.31	3.13
	PHP(−)	1.23	2.06	−0.24	2.70
	Surgical	1.96	2.29	1.20	2.71
	Control	0.98	2.03	0.22	1.74

PHP(+) $N = 28$, PHP(−) $N = 10$, Control $N = 30$, PHP(+): posterior hyaloid peeling group, PHP(−): posterior hyaloid non-peeling group, Std: standard deviation, CI: confidence interval.

Table 3. Vein Diameter Percentage Ratio Results

Vein Region	Group	Mean	Std	95% CI Lower	95% CI Upper
ST	PHP(+)	8.68	7.97	5.89	11.46
	PHP(−)	3.51	4.21	0.50	6.52
	Surgical	7.50	7.57	5.20	9.80
	Control	0.11	0.31	−0.03	0.25
IT	PHP(+)	7.18	6.29	4.98	9.37
	PHP(−)	2.63	4.48	−0.57	5.84
	Surgical	6.15	6.19	4.27	8.03
	Control	0.09	0.31	−0.05	0.23
ST + IT	PHP(+)	7.93	6.59	5.63	10.22
	PHP(−)	3.07	4.17	0.09	6.06
	Surgical	6.82	6.42	4.87	8.77
	Control	0.10	0.28	−0.03	0.22

PHP(+) $N = 34$, PHP(−) $N = 10$, Control $N = 21$, ST: superior temporal, IT: inferior temporal, ST + IT: average of superior temporal and inferior temporal, PHP(+): posterior hyaloid peeling group, PHP(−): posterior hyaloid non-peeling group, Std: standard deviation, CI: confidence interval.

0.98 ± 2.03, $P = 0.093$). However, the PHP(+) group had significantly higher values compared to the control group (2.22 ± 2.35 vs. 0.98 ± 2.03, $P = 0.029$), whereas the PHP(−) group demonstrated no significant difference (1.23 ± 2.06 vs. 0.98 ± 2.03, $P = 0.914$; see Table 2).

Vein Diameter Percentage Ratio Results

There is a significant increase in ST (7.50 ± 7.57 vs. 0.11 ± 0.31, $P < 0.001$), IT (6.15 ± 6.19 vs. 0.09 ± 0.31, $P < 0.001$), and ST + IT (6.82 ± 6.42 vs. 0.10 ± 0.28, $P < 0.001$) measurements in the surgical group compared to the control group. Similarly the PHP(+) group has significantly higher ST (8.68 ± 7.97 vs. 0.11 ± 0.31, $P < 0.001$), IT (7.18 ± 6.29 vs. 0.09 ± 0.31, $P < 0.001$), and ST + IT (7.93 ± 6.59 vs. 0.10 ± 0.28, $P < 0.001$) values compared to the control groups, as well as the PHP(−) group ST (3.51 ± 4.21 vs. 0.11 ± 0.31, $P < 0.001$), IT (2.63 ± 4.48 vs. 0.09 ± 0.31, $P = 0.001$), and ST + IT (3.07 ± 4.17 vs. 0.10 ± 0.28, $P < 0.001$) values. A significant difference exists between the PHP(+) and PHP(−) groups for ST (8.68 ± 7.97 vs. 3.51 ± 4.21, $P = 0.005$), IT (7.18 ± 6.29 vs. 2.63 ± 4.48, $P = 0.001$), and ST + IT measurements (7.93 ± 6.59 vs. 3.07 ± 4.17, $P = 0.002$; Table 3, Fig. 3)

Discussion

We observed a red shift in the ONH color and an increase in retinal vein diameter after vitrectomy, indicating an increase in ONH and retinal perfusion. Because the colorimetric data were corrected to all known confounding pigments in the eye and the illuminance differences induced by photography, we attribute

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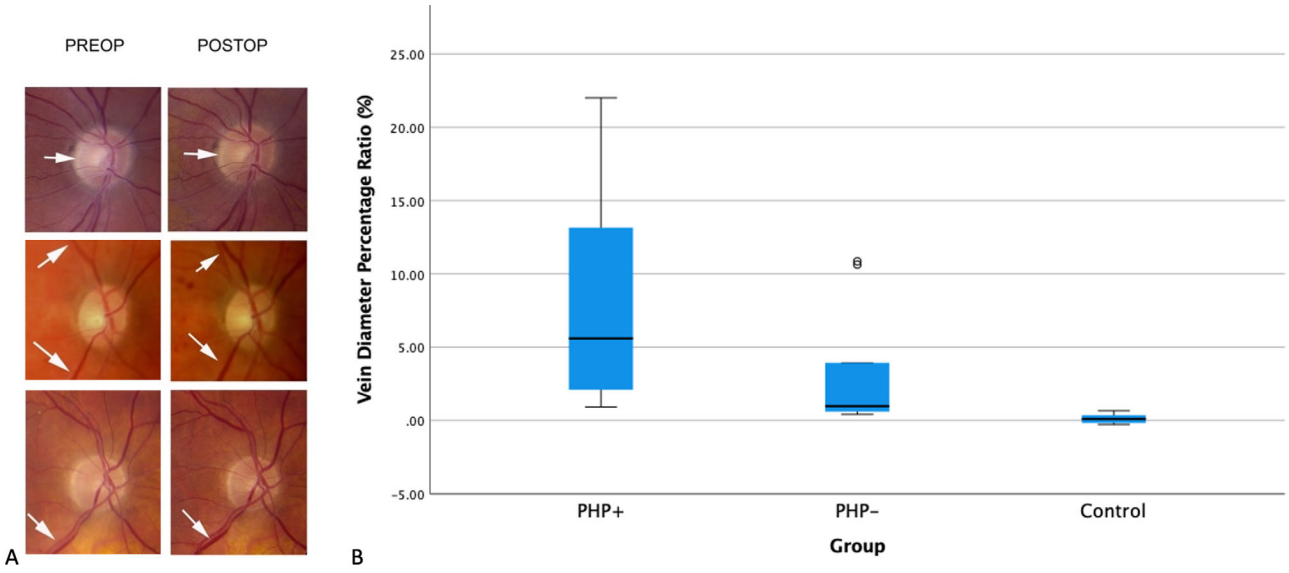


Figure 3. (**A**) Three examples of preoperative and postoperative optic disc images for the surgical group. After vitrectomy, improved optic nerve head and retinal blood flow manifests with the disappearance of optic nerve pallor and dilation of retinal vessels (*arrows*). (**B**) Vein diameter percentage ratio boxplot graph for groups. PHP(+): posterior hyaloid peeling group; PHP(−): posterior hyaloid non-peeling group; PREOP: preoperative; POSTOP: postoperative; %: percent.

this change to increased hemoglobin flux into the tissue. We found that this shift can be translated to an approximately 2.8-fold increase in ONH blood perfusion compared to controls. Studies using a different methodology confirmed our findings in various clinical settings.[20–24,36]

The beneficial impact of vitrectomy on several ischemic diseases has classically been attributed to the increased diffusion of ionic oxygen into the vitreous cavity.[37] Herein, we revealed another mechanism of how vitrectomy can improve retinal oxygenation. Retinal vessels have autonomic control and constrict upon exposure to increased oxygen.[38] Contrastingly, we observed a colorimetric shift, indicating an increased blood flow. Because all patients' post-vitrectomy fundus photographs were obtained >3 months after the surgery, our observation cannot be explained by the short-term effects of the surgery, such as low postoperative intraocular pressure or the use of postoperative medications. Indeed, intraoperative manipulations, such as increased IOP, were shown to reduce retinal perfusion.[39,40] Thus, the observed improvement in blood flow after vitrectomy may bring a new perspective to explain the impact of vitrectomy and PH peeling in diabetic macular edema cases that remained unresponsive to anti-VEGF treatment[41] or in retinal vein occlusion.[42]

Results of our study indicate that vitrectomy can modulate the optic disc and retinal blood flow. Retinal vascular pathologies that undergo vitrectomy often suffer from morphological cellular alterations that impede retinal perfusion, such as thickened retinal basal membranes and chronic activation of the retinal glia.[43] Cellular proliferation in and around the posterior hyaloid and its age-related thickening and stiffening[44] exerts mechanical traction on the superficial retina and the neighboring retinal vasculature, resulting in an altered retinal flow. The cases included in this study all had vitreoretinal interface problems, such as vitreomacular traction (VMT), macular hole, or diabetic retinopathy, characterized by thickening of the posterior hyaloid.[45] Thus, it is reasonable to assume that removing the posterior hyaloid in these cases will relieve the mechanical stress on the retinal vessels and improve retinal blood flow. A similar effect on retinal microcirculation was reported in patients who had undergone vitrectomy and membrane peeling surgery for epiretinal membranes.[46] Thus, a possible explanation of our observation may be the relief of vitreoretinal traction on retinal vessels and subsequent facilitation of the retinal blood flow.[24] This view is also supported by our finding that the beneficial effect of vitrectomy on retinal perfusion is only seen if the posterior hyaloid is peeled. Such a differential effect was not observed for ONH, where there is no hyaloid membrane and cellular proliferation is rare.

Our findings may also explain the overlooked impact of vitrectomy and posterior hyaloid peeling in radial optic neurotomy and adventitial sheathotomy. These techniques were more effective in cases where the posterior was peeled intraoperatively,[22] indicating that

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the benefit obtained from these surgeries was mainly due to the improvement of retinal blood flow induced by vitrectomy and posterior hyaloid peeling.[47]

Retinal perfusion changes have classically been assessed by observing changes in clinical features, that is, the disappearance of macular edema, or by estimating the ocular blood flow rate with color Doppler imaging.[48] However, Doppler measurements can be affected by artifacts, impacting their accuracy and reliability, and may not fully represent tissue perfusion. We observed rapid improvement of retinal and ONH blood following the removal of the posterior hyaloid during vitrectomy (see Fig. 3A). Our method offers an easier and more comprehensive reflection of whole retinal blood perfusion changes than traditional methods.

Although colorimetric analysis offers a significant opportunity to track changes in ONH blood perfusion metrics, it has some limitations, primarily due to subject background and technical aspects. One limitation of colorimetric analysis is the impact of age and refractive errors on color changes in the ONH.[49] Previous research has shown that age and myopia can significantly affect ONH blood flow, indicating that these factors must be carefully considered when establishing the control group and interpreting the results.[49] Although using vein caliber to indicate blood flow dynamics has practical value in the clinic, it is prone to age- and co-morbidity-related alterations due to vessel wall thickening, which undoubtedly decreases blood flow within the blood vessel.[50]

There are reports about using deep learning approaches for colorimetric analyses of the ONH. These studies highlight the potential future direction in the search for new algorithms and formulas to evaluate retinal and ONH perfusion metrics.[51] Artificial intelligence has recently been used in assessing the blood in various organs[52,53] Similar to other ophthalmic imaging methods used to determine retinal blood flow changes with artificial intelligence and deep learning techniques,[54] our colorimetric analysis may establish the groundwork for assessing the blood flow changes in the ONH and the retina.

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