RELATIONSHIP BETWEEN MYOPIC CHOROIDAL NEOVASCULARIZATION ACTIVITY AND PERFORATING SCLERAL VESSELS IN HIGH MYOPIA

JORGE RUIZ-MEDRANO, MD, PhD,†‡ ELENA ALMAZAN-ALONSO, MD,* IGNACIO FLORES-MORENO, MD, PhD,* MARILUZ PUERTAS, MD,* MARÍA GARCÍA-ZAMORA, MD,* JOSÉ M. RUIZ-MORENO, MD, PhD*†‡§¶

Purpose: To study perforating scleral vessels (PSVs) in patients with high myopia using swept-source optical coherence tomography and to determine their relationship with myopic choroidal neovascularization (mCNV) and its activity.

Methods: Retrospective analysis of patients with high myopia (≥−6 D or ≥26 mm of axial length) using multimodal imaging. The presence of PSVs and mCNV was assessed using swept-source optical coherence tomography images (TRITON; Topcon Corporation, Japan).

Results: Five hundred sixty-four eyes from 297 highly myopic patients were studied. One hundred fifty-five eyes (27.5%) showed signs of mCNV while PSVs were found in 500 eyes (88.6%). Perforating scleral vessels were found in 93.5% (145/155) of eyes with mCNV, and they were under or in contact with the mCNV in 80.6% (117/145). The mean number of intravitreal injections received by patients with mCNV was 4.06 ± 4.17 along 66.9 ± 4.1 months of follow-up. The number of injections per year was 1.32 ± 1.56, the mean number of relapses was 1.11 ± 1.83, and the mean number of relapses per year was 0.25 ± 0.41.

Conclusion: Perforating scleral vessels are more common among highly myopic patients suffering from neovascular complications. Myopic CNV complexes that are coincident with PSVs on optical coherence tomography show higher rates of activity, needing more injections to control them and being more prone to relapses.

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Myopia affects more than 1.5 billion people worldwide and up to one third of them present high myopia. Both these conditions are expected to see their prevalence continuously rise in coming decades, with the logical increase of myopia-related complications. The prevalence of high myopia globally sits at 1% to 4%, according to different reports, with the highest rates seen in East Asia with a prevalence of up to 21.6%. Macular alterations caused by structural changes in the posterior pole of these eyes may lead to loss of visual acuity and have become one of the main causes of blindness, most prominently in East Asia, sitting in fourth place of the ranking of leading causes of legal blindness in Spain.

Among the different macular complications, choroidal neovascularization (CNV) is the most common cause of vision loss among patients with pathologic myopia. Although its etiology is still not fully understood and despite the marked thinness or even the absence of certain areas of the choroid in
highly myopic patients, the origin of myopic CNV (mCNV) is believed to be from choroidal vasculature. Studies from Ohno-Matsui et al and Quaranta et al showed the presence of retroocular vessels in highly myopic patients using indocyanine green angiography. This was possible, in part, thanks to the characteristically thin structures in the posterior pole of such eyes. Choroidal circulation is nurtured by 10 to 20 short posterior ciliary arteries (SPCAs) that penetrate the sclera around the optical nerve in emmetropic eyes, whereas this distribution seems altered in highly myopic eyes with posterior staphylomas with a peripheral shift of entry sites, which tend to be located at the edge of the scleral ectasia.

Optical coherence tomography (OCT) technical advancements, most notably swept-source OCT, have increased signal penetrance, thus lessening sensitivity reduction with depth and providing an improved visualization of deeper structures, going beyond the choroid and providing, in some cases, good quality images of the sclera, retrobulbar fat, and even vascular structures that penetrate the posterior pole of the eye. There have been several reports on the presence of perforating scleral vessels (PSVs) and their possible relation to the development of macular alterations included in the pathologic myopia spectrum, such as lacquer cracks, chorioretinal atrophy, and mCNV. The prevalence of PSV in highly myopic patients and its possible connection to myopic complications remain uncertain.

The purpose of this article was to describe the prevalence of PSV and establish their connection to myopic complications and evolution of mCNV in a series of eyes with pathological myopia.

**Patients and Methods**

This cross-sectional, noninterventional study included eyes from highly myopic patients who attended Puerta de Hierro-Majadahonda University Hospital, and it was performed in adherence to the tenets of the Declaration of Helsinki for research involving humans. The study protocol was reviewed and approved by the ethics committee of our hospital, and all included patients signed the appropriate informed consent. Patient inclusion criteria comprised the presence of high myopia defined by an axial length ≥26 mm and/or a spherical equivalent ≥6 diopters (D), clear ocular media, age ≥18 years, clear media, good imaging quality (>45 image quality score of DRI Triton swept-source OCT software), and the will to participate in the study. Patients suffering from any other ocular or systemic disease other than cataract or refractive surgery were excluded.

Patients’ clinical records were analyzed for demographical data and information on the number of intravitreal injections received, if any; date of the first intravitreal injection; duration of follow-up; and number of mCNV relapses defined as the number of times the patient needs to resume treatment after reaching a lack of activity of the neovascular complex of at least 1 month. Patients were monitored monthly and were under a pro re nata treatment regimen. CNV was subclassified depending on the distance from the foveal center as subfoveal (0–750 μm), parafoveal (750–1,250 μm), and perifoveal (1,250–1,500 μm). All patients underwent a complete ophthalmological examination at the date of their recruitment for the study that included best-corrected visual acuity, refraction and optical biometry (IOL Master; Carl Zeiss, Tübingen, Germany) to obtain axial length, slit-lamp anterior segment examination, Goldmann applanation tonometry, indirect fundus ophthalmoscopy, and a series of test of multimodal imaging. All examinations were performed in both eyes if they met the inclusion criteria.

**Multimodal Imaging**

Infrared reflectance and fundus autofluorescence were performed using Spectralis confocal scanning laser ophthalmoscopy (Heidelberg Engineering, Heidelberg, Germany). Fundus photography and swept-source OCT were performed in all patients using a Topcon Triton platform (Topcon Corporation, Japan). The structural OCT protocol included radial 12-mm scans centered at the fovea and containing 1,024 axial scans. The software’s automatic segmentation of the retina, from the inner limiting membrane to the retinal pigment epithelium, was visually checked and corrected, if necessary, in all eyes before data collection. Choroidal thickness was manually measured under the fovea and in four further points located 1,000 μm superior, temporal, inferior, and nasal to it. Fluorescein angiography and OCT angiography were performed in cases with suspicion of mCNV. Neovascular lesions were defined as active when elevations of retinal pigment epithelium were accompanied by intraretinal or subretinal fluid, blurred margins, and/or impossibility to identify the external limiting membrane.

The presence of PSV was defined using the methods previously described by Querques et al and Giuffrè et al by two masked, independent retina experts (Figures 1 and 2).
All analyses were performed using a statistical analysis program (SPSS, version 26.0, IBM-SPSS, Chicago, IL). A two-tailed $P$ value, $0.05$ was considered as statistically significant. Descriptive statistics were provided for normally distributed variables using the mean and SD for quantitative and n (percentage) for categorical variables. To assess the normality or nonnormality of the variables, the Kolmogorov–Smirnov test was performed. Demographic data, best-corrected visual acuity, and LA were compared between groups using the independent Student t test for normally distributed variables, chi-square test for normally distributed, and Fisher exact test for nonparametric categorical variables. The Kruskal–Wallis test was used to compare ordinal variables with categorical variables, and the Pearson correlation was used to determine the correlations for normally distributed variables. The results were expressed in $r$ and $P$ value.

**Results**

Six hundred eyes from consecutive high myopic patients were included. Eyes that did not meet all the inclusion criteria were excluded, finally obtaining a total of 564 eyes from a total of 297 patients. 71.5% patients were female (403/564). Other demographic characteristics of the total sample are given in Table 1.

Of the total 564 eyes, 155 (27.5%) showed signs of mCNV. The presence of PSVs was found in 500 eyes (88.6%). Only 10 eyes of the total (10/564) showed neither vessels nor mCNV.

Regarding the eyes with mCNV, PSVs were found in 93.5% (145/155) and those PSVs were under or in contact with the mCNV in 80.6% (117/145). Perforating scleral vessels were found to be neither in contact nor below the mCNV in 19.3% of eyes (28/145).

The mean number of IVIs that patients with mCNV received was 4.06 ± 4.17 across a span of 66.9 ± 4.1 months of follow-up. The number of injections per year was 1.32 ± 1.56, the mean number of relapses was 1.11 ± 1.83, and the mean number of relapses per year was 0.25± 0.41 (Table 2).

Analyzing the incidence of PSVs, there was a higher presence rate of PSV in those eyes with mCNV (145/155 vs. 335/490; $P < 0.05$) (Table 3). The number of relapses was significantly higher in these patients (1.16 ± 1.86 vs. 0.17 ± 0.41; $P < 0.01$) when compared with patients without PSVs. It was also noticeable that those patients with PSVs received a higher number of IVIs (injections/year) (1.32 ± 1.68 vs. 0.46 ± 0.34; $P < 0.01$) and showed a higher number of relapses during the follow-up (relapses/year) (0.26 ± 0.41 vs. 0.02 ± 0.06; $P < 0.01$) (Table 4).

On the other hand, the fact that these vessels were under or in contact with the mCNV does relate to a higher incidence of relapses ($P = 0.60$), a higher number of injections during time (injections/year) ($P = 0.52$), or a higher number of relapses per year ($P < 0.40$).

Regarding choroidal thickness, patients without mCNV showed a thicker choroid than those with mCNV (93.80 ± 87.73 vs. 49.24 ± 51.36 mm; $P < 0.01$). Regarding eyes with mCNV specifically, the choroid was also thicker in patients with relapses than those with none (61.33 ± 50.53 vs. 41.46 ± 45.71 mm; $P < 0.05$) and in those patients without PSVs (119.91 ± 134.66 vs. 76.90 ± 71.68 mm; $P < 0.05$).

The presence of PSVs was not correlated with age, axial length, or best-corrected visual acuity ($P = 0.495$, Fig. 1. Multimodal imaging study of a highly myopic patient suffering from mCNV and A3T1N2s stage myopic maculopathy. Fundus photography shows the presence of an atrophic mCNV (A). Optical coherence tomography (OCT) angiography allows for a detailed visualization of choroidal vessels around the CNV, where a possible feeder vessel is identified (B, arrowheads). Structural OCT shows a hyporeflective structure across the sclera under the CNV corresponding to a perforating scleral vessel (C, arrow).

Fig. 2. Structural optical coherence tomography scan of an A4T2N2s highly myopic patient suffering from an atrophic CNV where two perforating scleral vessels are identified underlying the CNV scar (arrows).
in highly myopic eyes that develop pathologic myopia.

The posterior sclera in areas with patchy atrophy. More located at the edge of marked changes of curvature of retrobulbar vessels that perforate the sclera, usually

| Variable          | Mean     | Range    | SD  |
|-------------------|----------|----------|-----|
| Age (years old)   | 61.89    | 18–97    | 13.87 |
| Axial length (mm) | 29.44    | 20.00–37.60 | 2.44 |
| BCVA (Snellen)    | 20/30    | 20/20,000–20/20 |
|                  | 37       | 20       | 63  |
| Choroidal thickness (µm) | 81.50 | 0–476    | 81.70 |
| nº PSVs           | 2.94     | 1–9      | 1.35 |

P = 0.078, and P = 0.674, respectively). There was no statistically significant correlation between age and number of injections (P > 0.05) or age and number of relapses (P > 0.05).

A subanalysis on the presence of PSV depending on mCNV location was performed (Table 5). No statistically significant differences were found (P > 0.05).

### Discussion

Despite the extreme choroidal thinning taking place in highly myopic eyes that develop pathologic myopia, the development of a neovascularization complex is still believed to grow from choroidal vessels, although its actual pathogenesis is yet to be entirely elucidated, with mechanical, hemodynamic, and heredodegenerative theories trying to explain its process. In fact, some cases show a practical disappearance of choroidal tissue with sparse, isolated, bigger vessels being the only remnants of this layer. Latest technical advancements together with the thinness of posterior pole tissues in highly myopic patients allow for a good visualization of deeper structures, which has led to several findings. Back in 2012, Ohno-Matsui et al described the presence of hyporeflective structures at the level of the sclera, corresponding to long PCAs and SPCAs and differentiated between them based on their branching pattern on indocyanine green angiography images, with perforating structures going through the sclera and reaching the choroid. Likewise, Pedinielli et al described retrobulbar vessels that perforate the sclera, usually located at the edge of marked changes of curvature of the posterior sclera in areas with patchy atrophy. More recently, the same group reported the presence of dilated subfoveal choroidal veins (DCVs) below or around the neovascular complex in 30% of the eyes with mCNV. The authors suggested that mCNV receive the flow from the SPCA and drain to the dilated subfoveal choroidal veins. They stated that SPCAs are filled first, followed by mCNV, which then drain to the dilated subfoveal choroidal veins, and talked about the possible role that chronic choroidal venous congestion may play on the development of mCNV in eyes with PM.

Querques et al reported the presence of PSV in 37 of the 45 patients with lacquer cracks they studied (82%). They hypothesized that, although it might be coincidental, the high prevalence of PSVs under lacquer cracks might be the cause, or one of the causes, of the stretching of the tissue leading to their formation, caused by local scleral expansion. Highly myopic eyes with long axial length would be predisposed to suffering these mechanical breaks at the level of Bruch membrane that ultimately lead to alterations such as posterior pole hemorrhages or mCNV.

Giuffré et al found PSVs under 70.7% of their cases with mCNV and stated that they could play a role in neovascular development. The mean number of visible PSVs was 2.1 ± 1.0 in their series. Thirty-eight percent of the eyes with PSVs showed neovascular activity, whereas 62.1% of them did not. Among the eyes with no PSVs visible, 50% of them showed active CNVs and 50% showed inactive lesions. More interestingly, no statistical association was found between the presence of PSV and CNV activity (P = 0.4) because PSVs were present among 64% of active eyes and 75% of eyes with inactive lesions. No association was reported between PSVs and neovascular location either.

More recently, Xie et al reported a prevalence of PSVs of 80% among eyes diagnosed with mCNV. They stated that several factors may potentially play a role in the development of this complications, with relatively thinner choroids, thicker scleras, and PSVs among them. The imbalance in the thinning of sclera and choroid with the additional stress locally induced by the entrance of PSV is hypothesized to be a possible explanation for mCNV appearance.

Following the same line of investigation, Ishida et al reported a prevalence of PSV around the location of mCNV in 93 of 124 highly myopic eyes studied (75%). Ten of those cases showed PSVs in a

### Table 1. Demographics

| Variable          | Mean     | Range    | SD  |
|-------------------|----------|----------|-----|
| nº injections      | 4.06     | 0–22     | 4.17 |
| Months of follow-up| 66.9     | 4–216    | 44.1 |
| Injections/year    | 1.32     | 0–7.44   | 1.56 |
| nº relapses        | 1.11     | 0–9      | 1.83 |
| nº relapses/year   | 0.25     | 0–1.92   | 0.40 |
continuous location to the neovascular complex, whereas the other 83 communicated with the CNV through a thin segment of the remaining choroid. According to the stage of the CNV, the prevalence of PSV was 75% (9/12) in active lesions, 64.7% (33/51) in CNVs in the scar stage, and 83.6% (51/61) in atrophic CNVs. These differences were not statistically significant. An indocyanine green angiography was performed in 34 of the 93 eyes that showed PSVs, which were visible during the arterial phase of the angiogram. The authors concluded that the origin of these intrascleral vessels laid on SPCAs. None of the cases studied showed a macular vorticose vein, as previously reported. This supports the hypothesis that CNVs are not likely fed by the thin choroid found in these patients but more likely by other sources such as PSVs coming from SPCA.

This study reports a prevalence of mCNV of 155 of the 564 highly myopic eyes studied (27.5%), whereas 500 of them showed PSVs (88.6%). Taking into account the eyes with mCNVs, the prevalence of PSVs rose to 93.5% (145/155) in the same line but slightly higher than what had previously been described. Location wise, PSVs were found to be under or in contact with the mCNV in 80.6% (117/145), whereas they were found to be neither in contact nor below them in 19.3% of eyes (28/145).

More interestingly, the presence of PSV seemed to have an influence on mCNV activity, and they were significantly more prevalent in patients suffering from mCNV when compared with those not showing neovascular signs (145/155 vs. 335/490, respectively). Patients with PSVs needed more injections to treat their mCNV, receiving a mean 1.32 ± 1.68 injections per year when compared with the 0.45 ± 0.33 needed by those patients with mCNV but without visible PSVs; these differences being statistically significant. Furthermore, the absolute number of relapses was significantly higher in these patients when compared with patients without PSVs (1.16 ± 1.86 vs. 0.17 ± 0.41), showing a higher number of relapses per year (0.26 ± 0.40 vs. 0.02 ± 0.06; Table 4). On the other hand, the location of these vessels under or in contact with the mCNV did not influence the incidence of relapses ($P = 0.60$), the number of injections in time (injections/year; $P = 0.52$), nor the number of relapses per year ($P < 0.40$).

The higher activity rates shown by patients with PSVs could potentially be explained by the source that feeds to the neovascular complex. While a common myopic neovascular membrane feeds from a usually paper-thin choroid, PSVs and their reported connection to SPCAs$^{9,16}$ would theoretically provide a higher blood flow, which would translate into more active CNVs that would at the same time be more prone to reactivation in time after a correct response to antivascular endothelial growth factor drugs. To the best of our knowledge, this is the first study that reports and increase of mCNV activity in relation with the presence of PSVs.

This study has several limitations, though. indocyanine green angiography was not performed to confirm the origin of the intrascleral vessels seen on structural OCT images. This concept and the potential connection between SPCA and PSVs were based on previous publications by other authors.$^{9,16,18,23}$ This study’s database may be biased because patients attending the myopia unit of a tertiary referral center may not reflect the general myopic population. Further studies with larger samples will be necessary to corroborate our results.

In conclusion, PSVs are more common among highly myopic patients suffering from neovascular complications. Myopic CNV complexes that are coincident with PSVs on structural OCT images show higher rates of activity, needing more injections to control them and being more prone to relapses.

**Key words:** high myopia, myopic choroidal neovascularization, pathologic myopia, perforating scleral vessels, CNV, myopia, optical coherence tomography.
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