Areas of Nonperfusion in Peripheral Retina of Eyes With Pathologic Myopia Detected by Ultra-Widefield Fluorescein Angiography

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PURPOSE. We investigated the vascular system in the far peripheral retina in eyes with pathologic myopia by ultra-widefield fluorescein angiography (FA).

METHODS. We analyzed retrospectively 230 with pathologic myopia (myopic refractive error >8 diopters [D] or axial length >26.5 mm) and 42 emmetropic (refractive error <±2 D) controls who were examined with ultra-widefield FA by the Optos P200 system. Far peripheral retina was defined as the area anterior to the ampullae of the vortex veins.

RESULTS. Retinal capillary telangiectasia was observed in the far periphery of 34 of 42 (81.0%) emmetropic eyes and in 90 of 115 (78.3%) highly myopic eyes. Retinal capillary microaneurysms were observed in 13 of 42 (31.0%) emmetropic eyes and in 60 of 115 (52.2%) eyes with pathologic myopia. The differences in the incidences of these two lesions were not significant. Areas of nonperfusion in the far periphery were found in two of 42 (4.8%) emmetropic eyes and in 95 of 115 (82.6%) eyes with pathologic myopia. In these myopic eyes, the arterioles and venules had an abrupt ending, and in advanced cases, the perfused area was limited to just beyond the staphyloma border. None of the eyes developed retinal neovascularization. Statistical analyses showed that the highly myopic patients with avascular areas in the far periphery were significantly older, and had significantly longer axial length.

CONCLUSIONS. Areas of nonperfusion in the far periphery are common in eyes with pathologic myopia. Retinal vasculature in the far periphery is significantly altered in eyes with pathologic myopia, and this may be due to a mechanical stretching.

Keywords: pathologic myopia, peripheral retina, wide-field angiography

Pathologic myopia is characterized by an excessive increase in the axial length of the eye and formation of posterior staphyloma(s).1 Eyes with pathologic myopia also have different kinds of lesions in the posterior pole, including myopic choroidal neovascularization, myopic tractional maculopathy, myopic optic neuropathy, and myopic chorioretinal atrophy.2–4 We recently reported that the shape of eyes with pathologic myopia is deformed, and the eyes are not spherical as they are in emmetropic eyes.7,8 The eye shape was divided into four distinct types; nasally-distorted type, temporally-distorted type, cylinder type, and barrel type.7 The results of these studies indicated that pathologic myopia is a disorder that affects the shape of the entire globe, including the near peripheral areas; that is, just beyond the equator. These findings indicated that the lesions associated with pathologic myopia were not confined to the posterior pole of the eye.

It has been reported that most of the growth of the axial length of the eye during the emmetropization process is due to a growth of the peripheral regions of the eye.9,10 In our High Myopia Clinic, we noticed ophthalmoscopically that some patients with pathologic myopia had small retinal hemorrhages in the far peripheral fundus; that is, beyond the equator. This suggested that retinal vascular abnormalities may develop in the far periphery of highly myopic eyes, but it was difficult to document these lesions with standard fundus cameras. This difficulty has been overcome by a relatively new instrument, the Optos Optomap Panoramic 200A Imaging System (Optos, PLC, Dunfermine, Scotland). This instrument combines an ellipsoid mirror and a scanning laser ophthalmoscope (SLO), and can obtain panoramic fundus images with a field of approximately 200°. The Optos system can be used for ultra-widefield fluorescein angiography (FA) during which the central and peripheral retina are photographed simultaneously without the need of turning the eye. With these capabilities, ultra-widefield FA has been able to detect abnormalities in the far periphery of eyes with various retinal diseases.11–17 However, eyes with high myopia have not been examined by ultra-widefield FA to our knowledge.

Thus, the purpose of this study was to determine whether retinal vascular abnormalities were present in the far periphery of eyes with pathologic myopia. To accomplish this, we performed ultra-widefield FA with the Optos system on 238 eyes with pathologic myopia. PATIENTS AND METHODS

Subjects

The procedures used conformed to the tenets of the Declaration of Helsinki, and their use was approved by the...
Ethics Committee of the Tokyo Medical and Dental University. A written informed consent was obtained from all of the patients.

We studied retrospectively 119 consecutive patients (238 eyes) who were examined in the High Myopia Clinic at Tokyo Medical and Dental University between March 2012 and October in 2012. All of the eyes were diagnosed with pathologic myopia, which was defined as a myopic refractive error (spherical equivalent) of >8.0 diopters (D) or an axial length ≥26.5 mm. For controls, 42 consecutive patients with emmetropia who were examined at the Nagoya City University Hospital or Tokyo Medical and Dental University between February 1 and October 30, 2012 were studied. Emmetropia was defined as a refractive error (spherical equivalent) of ≤±2.0 D. Ultra-widefield FA was performed on these latter eyes because they were the normal eyes of patients with unilateral age-related macular degeneration (AMD) or unilateral central serous chorioretinopathy (CSC).

Patients with systemic diseases that could affect the retinal vasculature, such as hypertension, diabetes, hyperlipidemia, and hypercholesterolemia, were excluded. Eyes with or a history of retinal vascular occlusive diseases, such as retinal artery or vein occlusion, retinopathy of prematurity, or retinal vasculitis, also were excluded. In addition, eyes that had undergone vitrectomy surgery also were excluded.

All of the participants had comprehensive ocular examinations, including refractive error measurements and axial length measurements using the IOL master (Carl-Zeiss, Tubingen, Germany). The refractive error was measured with an autorefractometer (ARK-730; Nidek, Aichi, Japan) without cycloplegia.

Ultra-Widefield FA

Ultra-widefield FA was performed with an intravenous injection of 5 mL of 10% sodium fluorescein. The images were recorded with an Optos 200Tx scanning laser ophthalmoscope (Optos PLC). The images in the venous phase at 1 minute after dye injection were used for the analyses of the retinal vasculature in the far periphery. The far peripheral retina was defined as the area between the ampullae of the vortex veins and the ora serrata. The widefield color images and widefield FA images were used to identify the vortex vein ampullae, which were located near the ocular equator. These locations were marked on the FA montages. In emmetropic eyes, the images of the far peripheral retina were taken by instructing the patients to gaze leftward or rightward (Fig. 1), whereas it was possible to observe far peripheral retina without gazing leftward or rightward in all of the highly myopic patients. The superior and inferior peripheral retinal images were difficult to obtain, because of the upper and lower eyelid and eyelash. Thus, we only analyzed the far periphery in the horizontal plane; that is, the nasal and temporal retina (Fig. 2).

Two of the authors (MM and KOM) who were masked to the refractive status of the eye checked the FA findings of the far peripheral retina, and an agreement of the two authors was obtained for all of the images.

Statistical Analyses

The significance of the differences in patients’ age, refractive error, and axial length, was determined by the Mann-Whitney U test. The distribution of the sexes, incidence of posterior staphyloma, and angiographic findings were compared by χ² tests. A P < 0.05 was considered statistically significant.
RESULTS

A total of 119 consecutive patients (238 eyes) with pathologic myopia had ultra-widefield FA with the Optos 200Tx system. Eight eyes (four patients) had an incomplete imaging of their retinal periphery and were excluded from the analysis. In the end, 230 eyes of 115 patients with pathologic myopia were studied, and the data of one randomly selected eye were used.

A total of 42 consecutive patients (42 eyes) with emmetropia with unilateral diseases examined by ultra-widefield FA served as controls. Of the patients 33 had unilateral AMD, seven had unilateral CSC, and two had unilateral metamorphopsia.

The clinical characteristics of all of the participants are shown in Table 1. The highly myopic patients were significantly younger than the emmetropic controls.

### Peripheral Retinal Vascular Findings in Eyes With Emmetropia

The retinal capillaries in the periphery had a clear ramified pattern in the far periphery in 34 of 42 emmetropic eyes.
Peripheral retinal vascular changes

<table>
<thead>
<tr>
<th></th>
<th>Emmetropia, 42 Eyes</th>
<th>Pathologic Myopia, 115 Eyes</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capillary not clearly visualized, eyes, %</td>
<td>0</td>
<td>0</td>
<td>N.S.</td>
</tr>
<tr>
<td>Capillary telangiectasia, eyes (%)</td>
<td>34 (81.0)</td>
<td>90 (78.3)</td>
<td>N.S.</td>
</tr>
<tr>
<td>Capillary microaneurysm, eyes (%)</td>
<td>13 (31.0)</td>
<td>60 (52.2)</td>
<td>0.03</td>
</tr>
<tr>
<td>Dye leakage from MA or telangiectasia, eyes (%)</td>
<td>0</td>
<td>33 (28.7)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Avascular area, eyes (%)</td>
<td>2 (4.8)</td>
<td>95 (82.6)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Retinal vascular anastomosis, eyes (%)</td>
<td>0</td>
<td>3 (2.6)</td>
<td></td>
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</table>

* x² test.

(81.0%), and these eyes were considered to have capillary telangiectasia (Fig. 3). Retinal capillary microaneurysms also were observed in 13 of the 42 emmetropic eyes (31.0%, Fig. 3), and all of these 13 eyes had retinal capillary telangiectasia around the microaneurysms. There was no dye leakage from the dilated capillaries or microaneurysms in emmetropic eyes.

In two of these 42 eyes (4.8%), an avascular area was found in the far periphery (temporal periphery in both eyes). The end of retinal arterioles and venules was observed only in 11 of 42 emmetropic eyes even though the patients were instructed to gaze rightward and leftward.

Far Peripheral Retinal Vascular Changes in Eyes With Pathologic Myopia

Retinal capillary telangiectasia was observed in the far periphery in 90 of 115 highly myopic eyes (78.3%, Fig. 4). The incidence of retinal capillary telangiectasia in the highly myopic eyes was not significantly different from that in emmetropic eyes (Table 2). The ramified pattern due to the capillary telangiectasia was seen more clearly and was located more peripherally in eyes with pathologic myopia than with emmetropia. Retinal capillary microaneurysms were seen in 60 of 115 pathologic myopia eyes (52.2%). These abnormalities also were observed in emmetropic eyes. Dye leakage from the microaneurysms or dilated capillary vessels was seen in 35 of 115 eyes (26.1%, Fig. 5).

Avascular Area in Far Peripheral Retina in Eyes With Pathologic Myopia

In 95 of 115 eyes (82.6%), an avascular area was found in the far periphery (Fig. 6). The avascular areas were observed significantly more frequently in the temporal periphery than the nasal periphery (82.6% vs. 41.7%). The eyes with avascular areas in the nasal periphery always had nonperfusion areas in temporal periphery as well. In some areas, the nonperfusion was observed only in capillaries between the arterioles and venules (Fig. 6). However in these eyes, the arterioles and venules also were occluded as observed by an abrupt ending of the retinal arterioles or venules (Fig. 7). In some patients, the perfused area was limited to the region around or just beyond the border of a staphyloma leading to a wide avascular area (Fig. 8B).

In three of the 115 eyes with a retinal avascular area in the far periphery, abnormal shunt vessels were observed (Fig. 9). In one eye, a retinal venule had an abnormal course with multiple branching giving it a radiating appearance (Fig. 10). None of the 95 eyes with avascular area in the far periphery had any evidence of retinal neovascularization. A comparison of the characteristics of the retinal vascular changes in emmetropic eyes and highly myopic eyes is presented in Table 2.

We then compared the factors that were significantly correlated with the presence of the avascular areas in the far periphery of eyes with pathologic myopia (Table 3). The highly myopic patients with avascular areas in the far periphery were significantly older, significantly more myopic, had significantly longer axial lengths, and had a posterior staphyloma significantly more frequently.

**DISCUSSION**

The ultra-widefield FA images obtained by Optos showed different kinds of abnormalities of the retinal vasculature in the far periphery of eyes with pathologic myopia. The abnormalities included large areas of nonperfusion by capillaries and larger vessels. Some of the pathologies, for example, capillary telangiectasia and microaneurysms, also were found in emmetropic eyes, although the degree of abnormalities was more severe in highly myopic eyes.

In normal eyes, the retinal capillaries are not clearly observed by FA in most areas of the fundus except around the foveal avascular zone. However, in the fluorescein angiograms obtained by Optos, the peripheral retinal capillaries generally were observed clearer than the capillaries in the posterior pole of most eyes irrespective of the refractive status. Spitznas and Bornfeld investigated the architecture of the most peripheral retinal vessels histologically in enucleated eyes or those obtained at autopsy, and they reported that the number of small vessels in the periphery was fewer, and the distribution of vessels was reduced to a single retinal layer; that is, the retinal ganglion cell layer or the nerve fiber layer. They
suggested that the peripheral vasculature was confined to a single layer because of the thinness of the peripheral sensory retina. Thus, in addition to the decreased thickness of the retina, the more superficial location of the vessels should allow the retinal capillaries to be observed more clearly in the far periphery.

Capillary telangiectasia and microaneurysms were found in emmetropic and highly myopic eyes, although the severity was different. Using astigmatic FA, Asdourian and Goldberg reported that the peripheral capillaries were considerably larger and were clearly more elongated than those of the posterior pole. In the far periphery, the capillaries were reduced to isolated loops connecting the arterioles and venules. Due to the special morphologic features of the peripheral retinal capillaries, it was not clear whether the ramified pattern seen in peripheral capillaries in our eyes represented normal capillaries or capillary telangiectasia. Although a clear distinction is difficult, the coexistence of microaneurysms, and dye leakage from microaneurysms and dilated capillaries in the areas of the ramified patterned capillaries suggested that this represents capillary telangiectasia at least in some cases.

The reason why retinal capillary telangiectasia and microaneurysms were found in emmetropic eyes as well as highly myopic eyes is not clear. We previously reported that capillary telangiectasia and microaneurysms developed in the macular area in eyes with myopic traction maculopathy (MTM), and these changes disappeared after release of macular traction by vitrectomy. This suggested a possibility that these changes were caused by mechanical damage onto the retinal capillaries at least in some cases, and we termed this condition “myopic traction retinal vasculopathy.” Although the location of these retinal capillary changes was different (posterior fundus versus far periphery), we consider that mechanical damage onto the retinal capillaries could cause similar vascular changes in the far periphery as well. However, this is our speculation, and this must be examined in the future.

It has been reported that most of the growth of the axial length during the emmetropization process is due to the growth of the peripheral section of the posterior segment. In vivo, digital imaging of the neonatal retina showed that most of the growth of the eye occurs in the equatorial region, while the visually critical part of the retina is relatively unperturbed during development. Ishii et al. analyzed the changes in the eye shape quantitatively by examining the magnetic resonance images in subjects at 1 month to 19 years of age and suggested that myopic axial elongation is a continuous process of emmetropization. Thus, a continuous elongation of the area around the equator might occur in highly myopic eyes when the axial length increases. The very end of the retinal capillaries was observed easily in highly myopic eyes without...
moving the direction of gaze. This also was possible because the eye expanded in the equator region.

An avascular area in the far peripheral retina was found in 82.6% of eyes with pathologic myopia, but in only 4.8% of emmetropic eyes. This suggested that peripheral avascularity is a characteristic of eyes with pathologic myopia. Among these eyes, the avascular area was found significantly more frequently in eyes with longer than shorter axial lengths. The reason why a wide avascular area is seen commonly in eyes with pathologic myopia was not determined; however, one possibility is that the vessel-free zone that normally exists in the far periphery becomes wider in eyes with pathologic myopia. Penman et al.23 reported that areas of nonperfused retina posterior to the margin of the vascular bed in the peripheral retina are found in a small number of normal children. However, the extent of the capillary dropouts was much smaller than that seen in this study. Rutnin and Schepens24 reported the presence of an area of 0.5 disc diameter (DD) of peripheral nonperfusion in normal adults by ophthalmoscopy. Asdourian and Goldberg20 used astigmatic FA to show the presence of approximately 1 mm (0.67 DD) of nonperfusion in 12 healthy young adults without any ocular pathologies. In full-term neonates, the extent of the retinal vasculature is variable, especially temporally and superiorly, where the peripheral avascular zone may be up to 1.5 mm in width.25 Blair et al.26 investigated the peripheral nonperfused retinal area in 23 children at ages 2 months to 13 years using the RetCam system. They reported that no ocular pathology was found, but the overall mean width of retinal nonperfusion in these pediatric eyes was ≤1.5 DD with a mean of 0.9 DD temporally and 0.6 DD nasally. In the present study, a peripheral avascular area was found only in 4.8% in emmetropic eyes. This might be because it still was difficult to visualize the far end of retinal arterioles and venules in emmetropic eyes, even though the

![Figure 8](http://iovs.arvojournals.org/pdfaccess.ashx?url=/data/journals/iovs/933471/) A wide area of peripheral nonperfusion in eyes with pathologic myopia. (A) Left fundus of a 62-year-old woman with refractive error of −22 D and an axial length of 30.6 mm showing a wide area of nonperfused retina circumferentially in the periphery. The retinal capillaries and the retinal arterioles and venules are not present and have an abrupt cut-off appearance. (B) Right fundus of a 78-year-old woman with an axial length of 29.0 mm shows a wide area of nonperfused retina circumferentially in the peripheral fundus. All of the retinal arterioles, venules, and capillaries were nonperfused beyond the vascular arcades temporally and nasally. A wide area of granular hyperfluorescence suggesting changes of the retinal pigmented epithelium is present in the peripheral fundus.

![Figure 9](http://iovs.arvojournals.org/pdfaccess.ashx?url=/data/journals/iovs/933471/) Abnormal shunt vessels in the far periphery. Left fundus of a 51-year-old woman with refractive error of −8.5 D and an axial length of 28.7 mm showing a formation of an anastomotic channel between venules in the temporal periphery (B, arrow). This vessel appears to be slightly dilated. Capillary telangiectasia is evident in the temporal periphery (B).
patients were instructed to gaze rightward and leftward when ultra-widefield FA was taken. Although measurements of the avascular area were not done in our study, the area of nonperfusion observed in peripheral retina in eyes with pathologic myopia seemed to exceed 1.5 DD. The larger area in highly myopic eyes could be because the retinal capillaries regress with an increase in the oxygen levels from the choroid due to a thinner peripheral retina.

In some cases, the capillary drop-out between the retinal arterioles and venules was patchy and similar to the avascular areas in the posterior pole of normal eyes. In more advanced cases, all of the retinal arterioles, venules, and capillaries were occluded, and the fluorescein angiograms showed an abrupt stoppage of blood flow. In extreme cases, the retinal vessels were obliterated just beyond the margin of posterior staphyloma (Fig. 8). Spaide12 reported the presence of peripheral nonperfusion in all of the patients treated with ranibizumab for central retinal vein occlusion (CRVO). He also reported that the capillary loss in the posterior pole of eyes with a CRVO was bordered by large, perfused vessels, but a widespread area of nonperfusion in the far periphery involved various-sized vessels, including arterioles, venules, and capillaries. The boundary between the posterior areas of perfusion and anterior areas of nonperfusion was abrupt as the arteries, veins, and capillaries appeared to be occluded within a narrow band. This appearance of the peripheral nonperfused area is very similar to what was found in the highly myopic eyes of our patients. Thus, this occlusion of vessels of different sizes; for example, arterioles, venules, and capillaries, might be a common feature of avascular areas in the far periphery. It is also possible that there was an extensive dropout of capillaries in a band-like fashion, which then would cause an obliteration of the larger vessels with an abrupt cut-off of blood flow. Whatever the cause is, none of the eyes with a nonperfusion area in the far peripheral retina developed retinal neovascularization. Although the reason for this is unclear, this is supported by the fact that angiogenic diseases, such as diabetic retinopathy, are less likely to develop in myopic eyes.27,28

Spitznas et al.18 found histologically that the vessels in the far periphery of the retina form very characteristic peripheral arcades. The arteries in these arcades can be followed to the veins without interposition of a vascular section resembling the capillaries as in the central retina. These circumferential vessels represented the terminal structures of the vascular system, because the retinal vessels existed in an end-arterial network. The location of the circumferential vessels may mark the area in the far periphery where the retina is thin enough to derive oxygen from the choroidal circulation. It is possible that some of the vascular arcades seen in the far periphery in our patients might be such circumferential vessels seen in normal eyes.

In addition to the presence of the circumferential vessels, the draining veins in the far periphery of some of our patients with pathologic myopia had an abnormal course (Fig. 10). These findings indicated that the retinal vasculature is changed beyond the near periphery over a wide area. It is less likely that such alterations are a simple exaggeration of the normal findings, but it seems to be a remodeling of the retinal vasculature due to the retinal vascular abnormalities.

This study has several limitations. Although we excluded patients with systemic diseases that could affect peripheral retinal vasculature, there still remains a possibility that the eyes of patients with other diseases that might affect the retinal vascular system were included. Also, the number of control eyes was limited because FA is an invasive examination and was considered unethical to perform FA on subjects without any retinal abnormalities. This is why the fellow eyes of the patients with unilateral AMD or CSC were included as normal controls, and it is not completely certain that these fellow eyes were completely normal. It also is possible that far peripheral image by Optos might be drawn out more in highly myopic eyes due to an increase of axial length than that in emmetropic eyes.

Despite the above limitations, the far peripheral retinal vasculature of highly myopic eyes was markedly different from that of emmetropic eyes. We concluded that ultra-widefield FA is a powerful tool for studying peripheral retinal vascular perfusion, and this technique has exposed the presence of a wide area of nonperfusion in the far periphery of eyes with pathologic myopia. This should be considered when we assess

### Table 3. Comparison of Eye and Clinical Characteristics of Highly Myopic Eyes With or Without Avascular Area in the Far Periphery

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Present</th>
<th>Absent</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, N patients, eyes</td>
<td>95</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>29</td>
<td>7</td>
<td>N.S.</td>
</tr>
<tr>
<td>Women</td>
<td>66</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Age, y old, mean ± SD (range)</td>
<td>61.6 ± 12.2 (27–80)</td>
<td>54.3 ± 14.4 (25–80)</td>
<td>0.03</td>
</tr>
<tr>
<td>Refractive error, D, mean ± SD (range)</td>
<td>−14.6 ± 4.8 (−6.5 to −24.5)</td>
<td>−10.5 ± 3.8 (−5.0 to −20.8)</td>
<td>0.001</td>
</tr>
<tr>
<td>Axial length, mm, mean ± SD (range)</td>
<td>30.1 ± 2.2 (24.9–36.9)</td>
<td>28.5 ± 1.5 (25.3–30.9)</td>
<td>0.002</td>
</tr>
<tr>
<td>Posterior staphyloma</td>
<td>68 (71.6%)</td>
<td>9 (45.0%)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

* Mann-Whitney U test.
not only the retinal circulation, but also the retinal lesions in eyes with pathologic myopia.

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**References**