Functional Loss in Age-Related Bruch’s Membrane Change With Choroidal Perfusion Defect

J. C. Chen, F. W. Firzke, D. Pauleikhoff, and A. C. Bird

During a prospective study of age-related macular degeneration, evidence of diffuse Bruch’s membrane disease was sought using fluorescein angiographic evidence of a prolonged choroidal filling phase. Dark-adapted static perimetry was done on eight eyes with this angiographic sign and on six eyes with a similar number of drusen but no manifest choroidal perfusion abnormality. Scotopic threshold was measured using the Humphrey automated perimeter and fine matrix mapping. In eyes without delayed choroidal perfusion, no discrete areas of increased threshold were found compared with the background sensitivity. By contrast, in seven of the eight eyes with fluorescein angiographic evidence of prolonged choroidal filling, discrete areas of scotopic threshold elevation (up to 3.4 log units) were recorded; these corresponded closely to regions of choroidal perfusion abnormality. It was postulated that diffuse deposits of abnormal material might account for both the perfusion abnormality and functional loss by acting as a diffusion barrier between the choriocapillaris and the retinal pigment epithelium. Invest Ophthalmol Vis Sci 33:334-340, 1992

There is a well-recognized association between those lesions causing visual loss in age-related macular disease, namely subretinal neovascularization and pigment epithelial detachments, and accumulation of debris in Bruch’s membrane.1-5 This debris collects either as discrete or diffuse deposits.5-9 Drusen are considered to be the clinical correlate of the discrete deposits; there is evidence that their form correlates both with the type of lesion likely to occur and with the magnitude of risk of visual loss.10-13 However, currently, no clinical signs are recognized suggesting the presence of the diffuse (linear) deposits. Therefore, the influence of such debris on disease cannot be studied clinically.

By analogy with Sorsby’s fundus dystrophy,14,15 a choroidal perfusion abnormality, as shown by fluorescein angiography, may indicate diffuse Bruch’s membrane disease in the aging eye.16 By contrast with the normal rapid filling of the choroid, in these eyes major choroidal blood vessels are seen before the choriocapillaris is filled, and the dye appears initially in the inner choroid as small points of fluorescence which gradually enlarge and coalesce over several frames of the angiogram.14,16 Continuous fluorescence, indistinguishable from the surrounding normal fundus, is not apparent until the venous phase of retinal circulation. Its appearance is similar to that seen in experimental ocular hypertension17 and in choroidal ischemia in humans.18-20 A causal relationship between this angiographic sign and the presence of diffuse Bruch’s membrane deposits has been postulated.14,16

During a prospective study of age-related macular disease, we documented angiographic evidence of prolonged choroidal filling.16 To establish the potential significance of this clinical sign, visual sensitivity was measured in eight eyes with this angiographic finding and in six eyes with a similar number of drusen but normal choroidal filling.

Patients and Methods

The patients were derived from the first 100 cases enrolled in a prospective study on age-related macular degeneration. Of these, 26 had evidence of a delayed and prolonged choroidal filling phase by fluorescein angiography.16 Eight eyes of eight patients with this angiographic sign and six eyes of six patients with no choroidal perfusion abnormality were studied. All eyes had a visual acuity of 6/12 (20/40) or better and drusen visible in the posterior ocular fundus. The appearance of the ocular fundus, visual acuity range, and age range were similar in the two groups. The mean visual acuity in the abnormal choroidal perfusion group was 6/8 (range, 6/5–6/12); in the normal choroidal perfusion group, it was 6/7 (range, 6/5–
Table 1. Patient data and summary of results of fine matrix mapping

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Visual acuity</th>
<th>Background threshold (log)</th>
<th>Discrete elevation (log)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>72</td>
<td>6/9</td>
<td>+</td>
<td>0.4</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>55</td>
<td>6/9</td>
<td>+</td>
<td>0.5</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>60</td>
<td>6/9</td>
<td>+</td>
<td>0.9</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>60</td>
<td>6/12</td>
<td>+</td>
<td>0.1</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>61</td>
<td>6/9</td>
<td>+</td>
<td>0.5</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>78</td>
<td>6/6</td>
<td>+</td>
<td>1.5</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>58</td>
<td>6/6</td>
<td>+</td>
<td>0.5</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>58</td>
<td>6/5</td>
<td>+</td>
<td>0.8</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>58</td>
<td>6/6</td>
<td>—</td>
<td>0.4</td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>61</td>
<td>6/6</td>
<td>—</td>
<td>0.6</td>
</tr>
<tr>
<td>11</td>
<td>F</td>
<td>72</td>
<td>6/6</td>
<td>—</td>
<td>0.4</td>
</tr>
<tr>
<td>12</td>
<td>F</td>
<td>54</td>
<td>6/6</td>
<td>—</td>
<td>0.8</td>
</tr>
<tr>
<td>13</td>
<td>F</td>
<td>72</td>
<td>6/6</td>
<td>—</td>
<td>0.8</td>
</tr>
<tr>
<td>14</td>
<td>F</td>
<td>67</td>
<td>6/5</td>
<td>—</td>
<td>0.9</td>
</tr>
</tbody>
</table>

* PCFP = prolonged choroidal filling phase.

In the abnormal choroidal perfusion group, the mean patient age was 63 yr (range, 55–78 yr); in the normal choroidal perfusion group, it was 64 yr (range, 54–72 yr; Table 1). There was no evidence of detachment of the retinal pigment epithelium, serous retinal detachment, or subretinal neovascularization in any eye. The study was supervised by the Hospital Ethical committee, and signed informed consent was obtained from each patient before entering the study.

Each patient was dark adapted for 45 min before scotopic static perimetry was done. Pupil dilatation of 6–7 mm was achieved by instilling one drop each of phenylephrine 10% and cyclopentolate 1%.

The scotopic threshold of the posterior central 30° was measured at 6° intervals using a modified central 30-2 program of the Humphrey automated perimeter (Allergan Humphrey, San Leandro, CA).21 With the background illumination turned off, the size V stimu-

lus was presented after passing it through the Humphrey blue filter (OCLI [Edinburgh, UK] dichroic long wavelength cutoff filter, 50% transmittance at 506 nm) mounted on a separate filter wheel with a 1.2 log unit neutral-density filter. An infrared source illuminated the bowl and an infrared CCD camera (Philips, Eindhoven, Holland) was used to monitor eye movements.

A more detailed study of scotopic retinal function was done using fine matrix mapping.22,23 This technique employs a television screen to present flashes of blue stimuli under scotopic conditions. The size of the stimulus, distance between subjacent stimuli, and size of the field tested are controlled by entering the desired parameters into the computer. A red light-emitting diode attached to the television screen for fixation can be moved, depending on the retinal area of interest. For our purposes, retinal sensitivity was tested at 100 positions on a 10 × 10 square matrix over a 20° × 20° test field, and stimuli were presented at 2° intervals with each stimulus subtending 10 min of arc. Subsequent processing of the data produced a three-dimensional representation of rod thresholds: the higher the elevation from baseline, the greater the loss of function compared with established normal values. The sensitivities were compared with the mean scotopic threshold of normal volunteers aged 30–42 yr.

To compare the sensitivity losses with the areas of delayed choroidal perfusion seen on the angiogram, a photographic print of the fluorescein angiogram was digitized at 256 × 256 × 8 bit resolution using a photon CCD camera (EEV, Chelmsford, UK), a Hawk V10 frame grabber board (Wild Vision, UK), and an Archimedes 440 RISC computer with ARM 3 processor (Acorn, Cambridge, UK). The area where the measurements of scotopic function were made was super-

Fig. 1. Fine matrix perimetry in a patient with drusen but normal choroidal filling showing a background threshold elevation of 1.0 log units (10 dB), but no major discrete threshold elevation. The small elevation of 0.2 log units (2 dB) close to fixation is often seen in normal individuals, and is thought to be due to luteal pigment and the reduced number of rod photoreceptors at the fovea.
Fig. 2. Montage of two-dimensional plots of sensitivity profiles recorded by fine matrix mapping. (A–H) are derived from patients 1–8, respectively, with a prolonged choroidal filling phase, and (I–N) from patients 9–14 with normal filling (Table 1). Contour steps: 0.1 log unit.
imposed on a corresponding $10 \times 10$ matrix grid on the fluorescein angiogram image where this fell in the circular aperture outline of the photograph. Each square of this matrix consisted of $17 \times 17$ pixels on the fluorescein angiogram image. The mean of 289 pixels was taken and used for comparison with the sensitivity measurements from the corresponding square of the fine matrix grid.

**Results**

Using the modified Humphrey automated static perimeter, a discrete area of scotopic threshold elevation of more than 1.0 log unit (10 dB) above normal was detected in six of eight eyes with a prolonged choroidal filling phase but in none of 6 eyes with drusen alone. These areas of abnormal threshold elevation in (1) eyes with choroidal filling abnormality and (2) suspicious areas of threshold elevation less than 1.0 log unit in other eyes then were selected for fine matrix perimetry testing.

On fine matrix mapping, eyes with normal choroidal filling had a mean scotopic threshold above normal of 0.7 log units (7 dB; range, 0.4–1.2 log units or 4–12 dB). Beyond $5^\circ$ from fixation, no discrete area of increased threshold above background levels was found (Table 1, Fig. 1).

Eyes with choroidal perfusion abnormality showed a mean background threshold above normal of 1.0 log unit (10 dB, Table 1). In addition, seven of these eight eyes also had discrete areas of scotopic threshold elevation above normal of 1.8 (18 dB) to more than 3.4 log units (34 dB, Fig. 2). The area of depressed sensitivity corresponded with the area of slow choroidal filling, and there was a quantitative correlation between the intensity of fluorescence during transit and threshold (Figs. 3, 4). One eye with minimal drusen and the angiographic sign of poor choroidal perfusion did not have an area of discrete threshold elevation.

**Discussion**

Although the number of patients involved in this study was small, our results strongly suggest that eyes with the angiographic sign of slow choroidal filling have a higher threshold than eyes with normal choroidal filling. Furthermore, areas of angiographic abnormality corresponded well with areas of discrete threshold elevation. Departure from perfect registry would be expected, given the imprecise quantitative nature of photographic recording of fluorescence. These findings support the proposal that this angiographic sign has significance in age-related macular disease.

Dark-adapted threshold elevation in the macular area in eyes with age-related macular disease has been documented by others. However, no correlation between the sensitivity and the number of drusen was found, and the threshold elevation over areas with and without drusen was similar. On the basis of these findings, it was concluded that more diffuse pigment epithelial or retinal dysfunction must be present other than that caused by drusen.

No established pathogenetic concepts are readily available to explain either the changes in choroidal fluorescence or the functional loss. Diminution of the
choroidal capillary bed with age has been shown by structural studies, but the absence of change in the arteries make it unlikely that it is caused by arterial obstruction or systemic hypertension. It is doubtful that capillary changes result from physical displacement by the debris because the same angiographic phe-
nomenon occurs in Sorsby's fundus dystrophy\textsuperscript{14} in which the deposits are internal to the inner collagenuous layer of Bruch's membrane.\textsuperscript{15} Furthermore, ob-
servations on acute and chronic choroidal ischemia
make it unlikely that there would be significant reti-
nal dysfunction as a consequence of the observed per-
fusion abnormality.\textsuperscript{19,29,30}

It has been suggested that a continuous layer of de-
bris in Bruch's membrane may act as a barrier to meta-
bolic exchange between the retinal pigment epithe-
lium and the choroidal capillaries.\textsuperscript{14,16} If this is true, it
might explain both the angiographic and psychophys-
ical findings observed in this and other studies. There
is circumstantial evidence that the behavior charac-
teristics of the choriocapillaris are determined by the
retinal pigment epithelium,\textsuperscript{31,32} and it has been pro-
posed that diffusible agents from the pigment epithe-
lium modulate the choroidal vasculature.\textsuperscript{33} Based on
these hypotheses, it was proposed that a barrier to
diffusion at the level of Bruch's membrane would re-
sult in changes in the choroidal capillaries.\textsuperscript{14,16}

Normal photoreceptor function depends on the
free diffusion through Bruch's membrane of large-
molecule complexes as they pass from the choriocap-
illaris to the pigment epithelium.\textsuperscript{34} Predictably, such
molecules would not pass freely through a continuous
layer of debris. This has been suggested as a mecha-
nism for the changes in proteoglycans in the interfiber
matrix of Bruch's membrane.\textsuperscript{35} However, the debris
deposited into Bruch's membrane by the retinal pig-
ment epithelium is likely to be a more important de-
terminant of conductivity. The magnitude of change
would depend on the thickness and chemical compo-
sition of Bruch's membrane, and the disturbance
would be particularly marked in the presence of a
large quantity of lipids.\textsuperscript{36}

Visual acuity and fundus appearance were identical
in patients with and without abnormal choroidal per-
fusion; neither clinical attribute segregated these two
populations. Although there are no simple clinical
cues to identify those patients with loss of scotopic
sensitivity, functional correlates were evident to the
patients. They reported the need for increased light
intensity for reading, fading vision after a few minutes
in bright light, slow recovery of vision after exposure
to bright light, and easy fatiguability when doing close
work.

To determine the significance of these findings to
the long-term outcome of age-related macular dis-
eease, a number of patients would have to be reviewed
longitudinally. By stratifying patients according to
characteristics of their drusen and fluorescein angi-
ographic evidence of prolonged choroidal filling phase,
a better index of Bruch's membrane disease might be
obtained, and better predictor of visual function and
prognosis might be achieved.

\textbf{Key words:} age-related macular degeneration, scotopic reti-
nal sensitivity, choroidal perfusion, Bruch's membrane, drusen

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