A Fluorescein and Indocyanine Green Angiographic Study of Choriocapillaris in Age-related Macular Disease

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Objective: To examine the phenomenon of a prolonged choroidal filling phase (PCFP) as seen on fluorescein and indocyanine green (ICG) angiography in patients with early age-related macular disease (AMD).

Methods: One hundred eyes of consecutive patients with early AMD were studied. Patchy and slow choroidal filling in early fluorescein and distinct areas of reduced choroidal fluorescence in ICG angiography were interpreted as PCFP. In addition, associated drusen characteristics and the AMD status of the fellow eye were recorded.

Results: A PCFP was observed in 26% of eyes using fluorescein and 32% of eyes using ICG angiography, with good concordance between findings using both techniques (κ = 0.9). A PCFP was associated with confluent drusen (P = .01), the presence of focal retinal pigment epithelial-atrophic patches in the study eye (P = .005), and geographic atrophy in the fellow eye (P = .03). Other drusen characteristics and the distribution of visual acuity (P = .90) were not different between eyes with and without PCFP.

Conclusions: A PCFP on fluorescein and ICG angiography is a common feature in early AMD. This sign has been interpreted as indicating reduced choroidal perfusion caused by change in diffusional characteristics of Bruch membrane. A PCFP is a clinical marker for diffuse deposits in Bruch membrane and a risk factor for the development of geographic atrophy.


In Sorsby fundus dystrophy, a prolonged choroidal filling phase (PCFP) occurs on fluorescein angiography. It is characterized by slow acquisition of fluorescence in the inner choroid during the early phase.1-3 This angiographic characteristic is similar to that seen in choroidal ischemia due to vascular disease4-9 and was interpreted as indicating choroidal hypoperfusion. It was postulated that this may be an indirect clinical indicator of diffuse deposits in Bruch membrane.10 A PCFP has been observed in age-related macular disease (AMD) as well, and similar conclusions were drawn as to the implications of this clinical sign.11

The rapid diffusion of fluorescein into the extravascular tissue makes it impossible to draw firm conclusions concerning intravascular flow on the basis of fluorescein angiography. In contrast, indocyanine green (ICG) diffuses only very slowly from choroidal capillaries and demonstrates the structure of the choroid in more detail.12 Our aim was to determine the prevalence of PCFP as an indicator of choroidal perfusion change in eyes with early AMD with confocal ICG angiography and to compare these results with the findings in simultaneous fluorescein angiography. In addition, associated AMD characteristics such as drusen and complications of late AMD in the fellow eye were analyzed.

RESULTS

Distinct areas with PCFP (Figure 2) were observed in 26 eyes (26%) with early AMD on fluorescein angiography (Figure 2, B) and in 32 eyes (32%) on ICG angiography (Figure 2, C). The concordance between the results of fluorescein and ICG angiography was good, with a κ value of 0.9.

The predominant ocular characteristic associated with PCFP was the presence of localized areas of RPE atrophy. This clinical finding was present in 28% of eyes with PCFP, and in only 6% of eyes without PCFP (Table [P = .005] and Figure 3).

In patients with PCFP in the study eye, the type of late AMD in the fellow eye was significantly more often geographic atrophy of the RPE. This manifestation of late AMD was present in fellow eyes of 25%
**PATIENTS AND METHODS**

One hundred consecutive patients with early AMD (12 patients with bilateral soft drusen; 88 patients with unilateral late AMD) underwent analysis. Informed consent for this investigation was given by each patient. The group consisted of 66 women and 34 men, aged from 60 to 92 years (mean age, 72.6 years). Visual acuity was measured using Early Treatment Diabetic Retinopathy Study charts. Color photography and simultaneous confocal fluorescein and ICG angiography were performed using a retina angiograph (Heidelberg Instruments, Heidelberg, Germany). A PCFP was defined as a distinct area of slow and patchy choroidal hypofluorescence during the early phase (first minute) of fluorescein angiography and as a distinct area of reduced diffuse background fluorescence during the early phase (first 3 minutes) of ICG angiography (Figure 1). Associated drusen characteristics (number, size, density, and fluorescence) were analyzed separately by 2 of us (D.P. and M.R.) using a grading system described in earlier studies, which have been shown to be reproducible. In addition, small, localized extrafoveal atrophic spots or proliferation of the retinal pigment epithelium (RPE) was recognized. The lesions in the fellow eye were classified as choroidal neovascularization, RPE detachment, or geographic atrophy of the RPE, including the fovea.

Potential associations were sought using \( \kappa \) statistics and \( \chi^2 \) test.

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**Figure 1.** Color photograph and fluorescein and indocyanine green (ICG) angiograms of a 68-year-old patient with early age-related macular disease (visual acuity, 20/30) show a central area of prolonged choroidal filling phase and atrophic spots at the temporal border of this area. A, Color photograph; B, early arteriovenous phase after 1 minute in fluorescein angiogram; C, simultaneous phase in ICG angiogram; and D, middle phase after 3 minutes in ICG angiogram.
of patients with PCFP in contrast to 4% of patients without PCFP (Table; \( P = .03 \)).

The only drusen characteristic associated with PCFP was a higher density of drusen in a central area surrounding the fovea (inside 1600 µm around the fovea) (Table; \( P = .01 \)). Drusen with distinct borders but direct contact (subconfluent) were present in 66% of eyes with PCFP vs 28% of eyes without PCFP, and confluent drusen were present in 19% of eyes with PCFP vs 9% of eyes without PCFP (Figure 4).

Visual acuity was not different between groups (\( P = .30 \)). The visual acuity in most of the study eyes was better than 20/40 (23 eyes [72%] in eyes with a PCFP vs 54 eyes [79%] in eyes without PCFP). In addition, no difference was found for other drusen characteristics (number, size, and intensity of fluorescence inside and outside 1600 µm and density outside 1600 µm) and irregular pigmentation at the level of the RPE.

Results of ICG angiography in our study support the conclusions drawn from fluorescein angiography findings that choroidal perfusion abnormality occurs in eyes with early AMD and good visual acuity. The correlation between findings using both techniques is very high. That more cases were found using ICG angiography is not surprising, since abnormal perfusion may be masked by leakage of dye during fluorescein angiography. The slow acquisition of fluorescence using sodium fluorescein had been ascribed to slow flow, alteration of leakage from the choroidal capillaries, or a combination of both. The results with ICG imply that slow flow contributes toward this clinical sign.

In Sorsby fundus dystrophy, a causal relationship between thickening of Bruch membrane and alteration of the choriocapillary layer has been proposed. It was argued that the normal angioarchitecture of the choriocapillary layer was dependent on the influence of growth factors produced by the RPE. From experimental studies of RPE cell cultures and of animals, there is good evidence that diffusible growth factors secreted by the RPE regulate the structure and functional characteristics of the choroidal vessels. A diffusion barrier created by thickening of Bruch membrane would alter concentration of growth factors in the inner choroid and consequently induce changes in the choriocapillary layer.

As with Sorsby fundus dystrophy, a causal relationship was postulated between structural changes in AMD. With age, there is reduction of the hydraulic conductivity of Bruch membrane that can be explained by thickening of Bruch membrane and the progressive accumulation of lipids therein. The cross-sectional area of the choriocapillaris also reduces with aging.

The observed association of PCFP with geographic atrophy is in accord with conclusions drawn from an earlier study. This could also be explained by biophysical changes in Bruch membrane if there is large impairment of metabolic exchange between the choriocapillaris and the RPE. The similarity of visual acuity between subjects with and without PCFP also has been described in other studies and indicates that neither...
the circulatory abnormality nor thickening of Bruch membrane influences suprathreshold function before the onset of geographic atrophy. However, threshold function is depressed in subjects with PCFP and good visual acuity in AMD and Sorsby fundus dystrophy. This interpretation received strong support from a clinical study that showed increase of threshold function in patients with Sorsby fundus dystrophy following dietary supplementation with beta carotene. That scotopic function should be affected more than photopic function is compatible with clinical and experimental observations.

It is biologically plausible that with progression of age changes in Bruch membrane and choroid, retinal atrophy would follow.

The association of subconfluent or confluent drusen with PCFP also may reflect Bruch membrane changes if passive diffusion of debris deposited into Bruch membrane by RPE toward the choroid is hampered, but some additional influence of large drusen blocking the choroidal fluorescence by thickened Bruch membrane cannot be excluded.

To what extent reduction of choroidal capillary flow contributes toward loss of visual acuity due to AMD is unknown, but should not be ignored as a clinical indicator of visual prognosis.

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Figure 4. Color photograph (A) and indocyanine green (ICG) angiogram (B-D) of a patient with confluent drusen (nonfluorescent in ICG) and a central area of prolonged choroidal filling phase (visual acuity, 20/20) (B, early phase after 1 minute; C, middle phase after 3 minutes; and D, late phase after 8 minutes).