Comparison between Optical Coherence Tomography and Fundus Fluorescein Angiography for the Detection of Cystoid Macular Edema in Patients with Uveitis

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Purpose: To compare optical coherence tomography (OCT) with fundus fluorescein angiography (FFA) for the detection of cystoid macular edema (CME) in patients with uveitis.

Design: Prospective comparative observational series.

Participants: One hundred twenty-one eyes of 58 patients with uveitis of varied causes (seven patients were studied twice).

Testing: Patients with suspected CME underwent OCT scanning followed by FFA at the same visit.

Main Outcome Measures: Detection and distribution of macular edema.

Results: One hundred eight eyes had similar results on both OCT and FFA in that 67 eyes had CME and 41 eyes had no CME. In 10 eyes subretinal fluid was detected on OCT but not FFA. Five of these eyes had CME on FFA but not OCT. Three other eyes had CME that was detected by FFA but not by OCT. Compared with FFA, the OCT sensitivity for detecting CME was 96% (including the eyes with subretinal fluid), and the OCT specificity was 100%.

Conclusions: OCT is as effective at detecting CME as is FFA but is superior in demonstrating axial distribution of fluid. *Ophthalmology 2000;107:593–599 © 2000 by the American Academy of Ophthalmology.*

Cystoid macular edema (CME) is a major cause of visual loss in uveitis, and considerable time and attention are devoted to its diagnosis.[1] At present, one of the most widely used investigations for confirming the presence of CME is fundus fluorescein angiography (FFA). This is an invasive test, with side effects ranging from nausea in up to 20% of cases to its rare complications of anaphylaxis and death.[2–5] The information it provides is qualitative and its interpretation can be highly subjective. Methods used to quantify macular edema have included confocal scanning laser ophthalmoscopy and the laser-based retinal thickness analyzers (Talia Technology Ltd., Mevaseret Zion, Israel).[6–9] The latter systems have been used either as a single green HeNe laser slit or as multiple scans to give a retinal map of surface topography computed from thickness measurements. The scanning laser ophthalmoscope (SLO) has been used to map the retinal surface, revealing relative changes in retinal surface height but not actual thickness.[6] The axial resolution of SLOs has been estimated at 300 μm, whereas the retinal thickness analyzer has a claimed depth resolution of 50 μm; in practice this may be degraded by scatter induced by retinal pathology.[8,10] The SLO measures changes at various depths and converts these into changes in the z-plane (depth of the retina), whereas the retinal thickness analyzer extrapolates the distance between two peak reflections on an angled laser slit into a measure of retinal thickness. The SLO has also been used to measure the area of retina in the x-y plane alone covered by cystoid spaces, but this requires injection of fluorescein dye.[7]

Optical coherence tomography (OCT) is a new method for high-resolution cross-sectional imaging of the retina that directly measures changes in the z-plane (depth of the retina).[11] It uses light to detect relative changes in reflection at optical interfaces by use of the method of low-coherence interferometry. It may be thought of as being analogous to B-scan ultrasonography, although it measures optical rather than acoustic reflection. OCT has been used to study a number of macular conditions including central serous chorioretinopathy, age-related macular degeneration, macular holes, macular edema, epiretinal membranes, and optic disc pit-associated maculopathy.[12–20] Its technical details have

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been described elsewhere, but for this article it should be remembered that OCT has a theoretical axial resolution of 10 to 14 μm.[11,12] Although there is a learning curve in both data acquisition and interpretation, it has been shown to have a high degree of reproducibility in measuring macular thickness in normal individuals and diabetic patients.[13] It is noninvasive, comfortable, and safe and can be repeated as often as is required. It is therefore ideally suited to repeated measurement of CME in conditions in which management decisions are required longitudinally on the basis of this information, such as uveitis. To evaluate its potential in determining retinal thickness in uveitic CME, we carried out a prospective study comparing the relative efficiency of OCT to detect CME in uveitic patients compared with the current standard of fluorescein angiography.

Table 1. Numbers of Eyes with Cystoid Macular Edema or Subretinal Fluid Detected by Optical Coherence Tomography or Fundus Fluorescein Angiography

	OCT	FFA
CME or SRF	77	75
No CME or SRF	44	46
CME on both	67	67
No CME or SRF on either	41	41
CME on FFA alone	—	3
SRF on OCT, CME on FFA	5	5
SRF on OCT alone	5	—

CME = Cystoid macular edema; FFA = fundus fluorescein angiography; OCT = optical coherence tomography; SRF = subretinal fluid.

Patients and Methods

Patients were recruited from the uveitis clinic at St. Thomas' Hospital, London, between January 1997 and March 1998, after Institutional Review Board/Ethics Committee approval was obtained. One hundred twenty-one eyes of 58 patients were included. Thirty-one patients had idiopathic retinal vasculitis (IRV), seven had sarcoidosis, five had intermediate uveitis, four had Behçet's disease, three had birdshot chorioretinopathy, three had Harada's disease, and there was one patient each with ankylosing spondylitis, polyarteritis nodosa, systemic lupus erythematosus, toxoplasmosis, and ulcerative colitis. Seven patients were examined on two occasions with greater than a 3-month gap and the separate visits were therefore included. All patients underwent a full ocular examination, including best-corrected distance (Snellen) and near visual acuity, slit-lamp examination, and indirect ophthalmoscopy. The visual acuities were converted to a logarithmic scale.[21] Slit-lamp examination included fundus examination with a 78 diopter lens (Volk Optical Inc, Mentor, OH) after dilatation with 1% tropicamide and 10% phenylephrine.

Those with suspected or known CME underwent OCT scanning (OCT 2000 scanner, Humphrey Instruments, San Leandro, CA) carried out by an experienced operator after informed consent was obtained. Four linear scans 3.01 mm in length were taken at 0, 45, 90, and 135 degrees centered on fixation. The images obtained have a laminar substructure with two bands of high-intensity signal. In previous publications the distance between the inner aspects of these bands has been assumed to give a measure of retinal thickness.[22] In many of these patients there were low-intensity spaces within the laminar substructure, and these were assumed to be cystoid spaces within the retina. Some patients had low signal spaces immediately anterior to the second high-intensity signal, and these were assumed to be subretinal fluid. The images were analyzed by counting pixels by use of the software calipers in Adobe Photoshop (Adobe Systems Inc, San Jose, CA) and averaged for the four scans. The pixels were counted for visible low-intensity spaces and for maximum retinal thickness. Five hundred pixels make up the 2-mm scan depth so that one pixel is 4 μm.

Fluorescein angiograms were taken subsequent to injection of 5 ml of 20% sodium fluorescein intravenously. Initially, stereophotographs of the macula were taken at approximately 3 minutes. In some patients, however, acceptable stereophotography was not possible owing to a combination of small pupil, media opacities, and poor fixation. Stereophotography was therefore abandoned, and the fluorescein angiograms were graded into five classes by the method of Yannuzzi et al[23,24] where grade 0 is no perifoveal hyperfluorescence, grade 1 is incomplete perifoveal hyperfluorescence, grade 2 is mild 360-degree hyperfluorescence, grade 3 is moderate 360-degree hyperfluorescence with the hyperfluorescent area being approximately 1 disc diameter across, and grade 4 is severe 360-degree hyperfluorescence with the hyperfluorescent area being approximately 1.5 disc diameters across.[23,24] All angiograms were graded by an experienced independent medical retina specialist who was masked to the OCT findings. Eyes in which media opacities prevented adequate visualization of the fundus for fluorescein grading were excluded.

Statistics

To assess reproducibility, three patients with representative examples of one each of relatively large cystoid spaces, relatively small cystoid spaces, and predominantly subretinal fluid on OCT scans had one horizontal OCT scan repeated five times at the same sitting (Figure 1). First, these scans were analyzed separately to assess consistency of scanning, and second, one scan each was analyzed on 5 separate days to assess consistency of analysis. The standard deviations were then divided by the means to give coefficients of variation.

The results of the OCT scanning and FFA grading were compared by use of Kendall's rank correlation.

Results

A summary of the results is shown in Table 1. Sixty-seven eyes had CME on both FFA and OCT (Figure 2). Eight eyes had CME detected by FFA but no intraretinal spaces on OCT. Five of these had subretinal fluid (SRF) on OCT, and the other three eyes all had grade 1 CME. Five other eyes had SRF on OCT that was not detected by FFA. Forty-one eyes had no CME on FFA or OCT. Overall there was good agreement between the two tests (Kendall's $\tau = 0.86$ for intraretinal cysts and 0.78 for all fluid, $P < 0.001$).

Fifteen of the eyes with CME on both FFA and OCT had SRF on OCT as well as intraretinal cysts. Nine had IRV, two had birdshot chorioretinopathy, and the other four had ankylosing spondylitis, Behçet's disease, Harada's disease, or systemic lupus erythematosus. Of the five eyes with SRF on OCT but CME on FFA, two had intermediate uveitis, two had IRV, and one patient had Behçet's disease. The three eyes with grade 1 CME on FFA but no detectable fluid spaces on OCT were one each of IRV, polyarteritis nodosa, and sarcoidosis. All five eyes with no CME on FFA but subfoveal SRF on OCT were from patients with Harada's

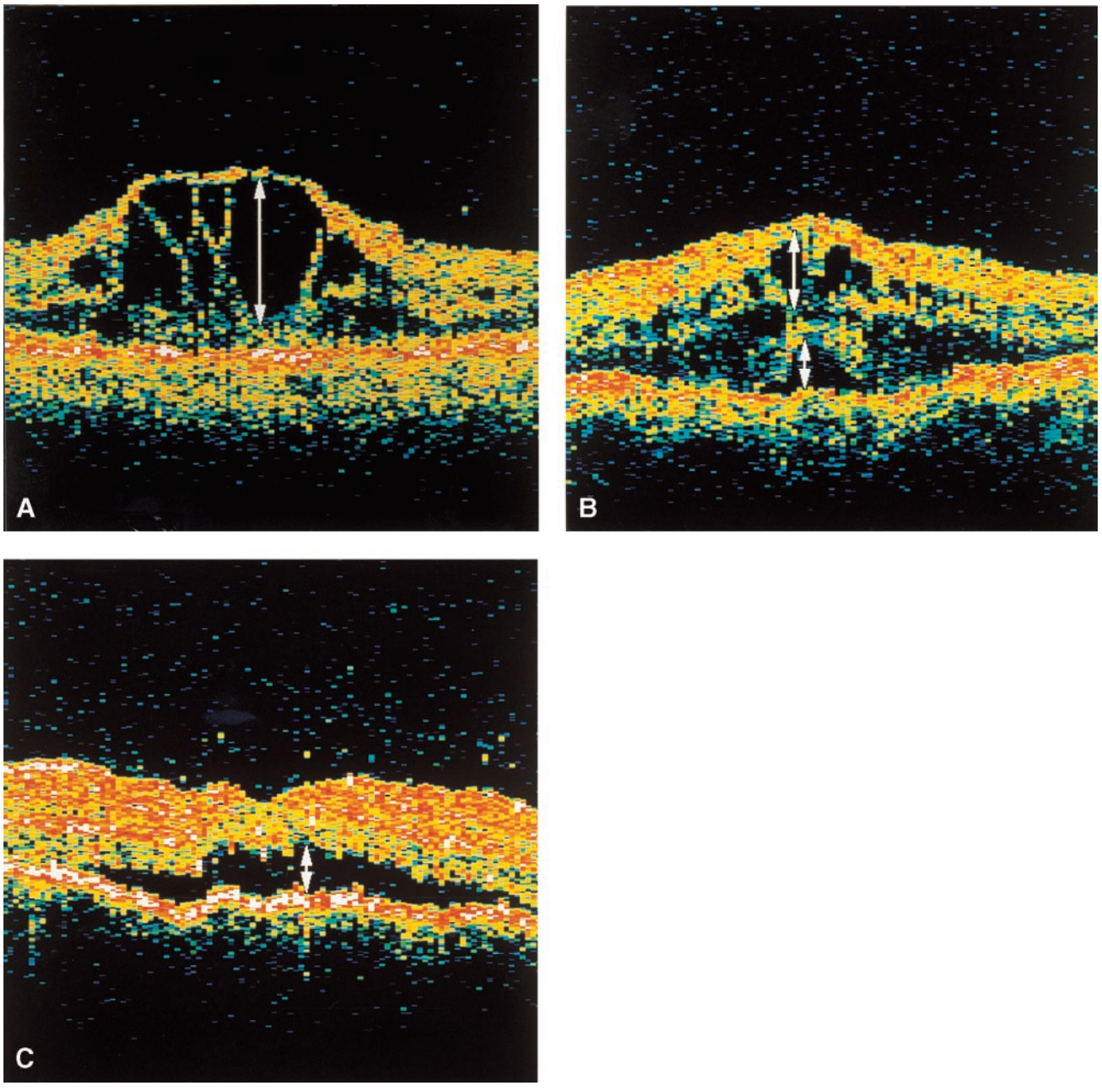

Figure 1. Examples of OCT scans repeated five times to measure coefficients of variation. White arrows show the low signal spaces measured. **A,** Large intraretinal cystoid space. **B,** Small cystoid spaces and some subretinal fluid. **C,** Low-signal space immediately anterior to the second high-intensity signal, which was assumed to be predominantly subretinal fluid.

disease, although they all had fluorescein leakage away from the fovea.

There was poor correlation between logarithmic visual acuity and both retinal thickness and cyst height measurements on OCT (adjusted $R^2 = 0.28$). When FFA was taken as the reference standard, the sensitivity of OCT was 89% for intraretinal cystoid spaces, increasing to 96% if the eyes showing subretinal low reflectance spaces were included, and the specificity of OCT for intraretinal cysts was 100%. The coefficients of variation were 13.5%, 12.5%, and 8.7% (standard deviation [SD] 60, 28, and 18 μm) for the five repeated scans of large cystoid space, small cystoid space, and subretinal fluid respectively (Fig 1), and 0.6%, 2.5%, and 4.4% (SD 4, 6, and 8 μm) for analysis of the same scan on separate occasions. For retinal thickness, the coefficients of variation were 0.8% to 2.9% (SD 5–16 μm) for five repeated scans and 0.5% to 1.1% (SD 4–11 μm) for analysis of the same scan on five separate occasions.

Discussion

Fluorescein angiography identifies breakdown of the blood-retinal barrier. Barrier breakdown precedes fluid-related thickening at focal sites, although previous studies have

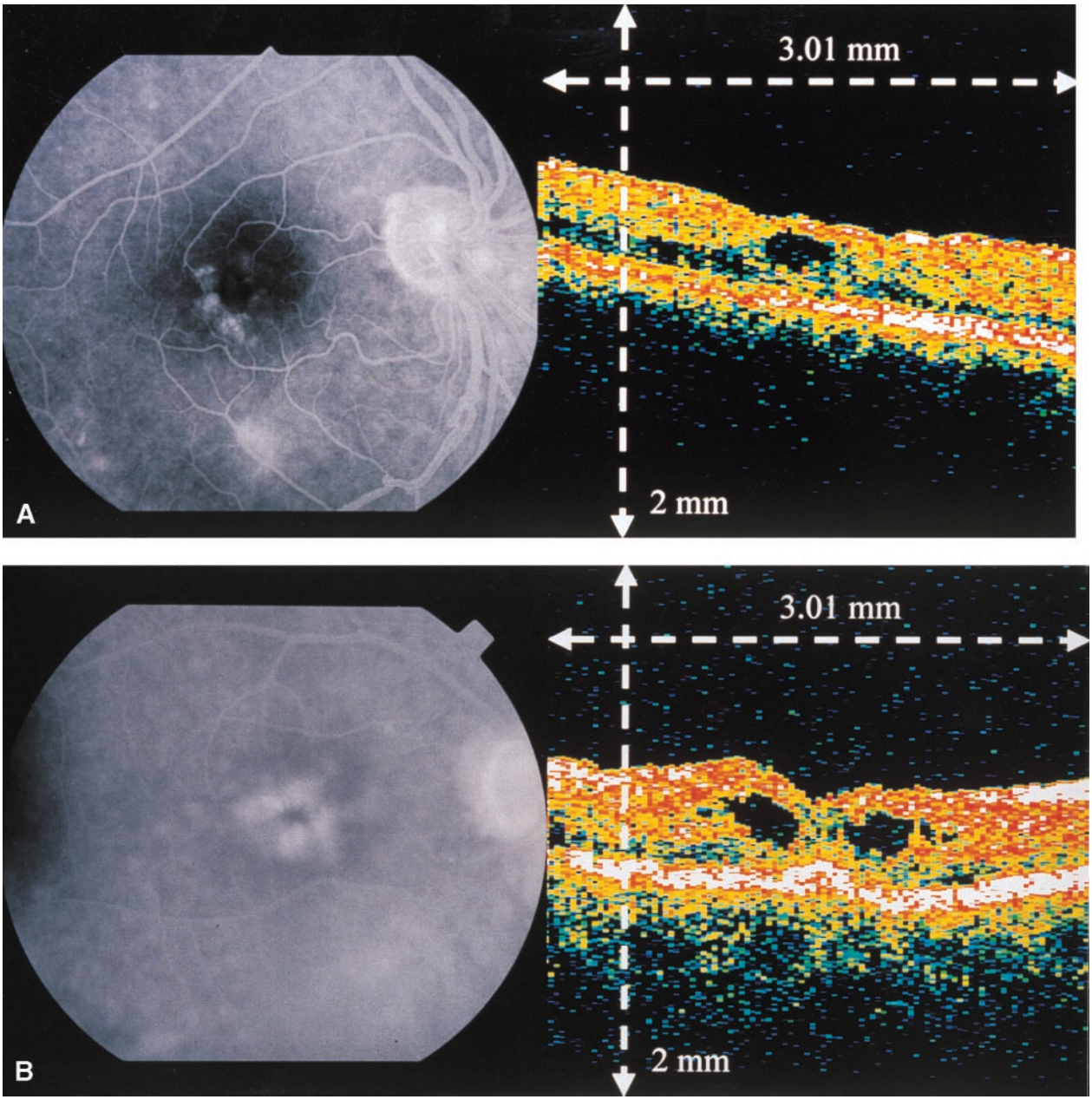

Figure 2. Examples of graded fluorescein angiograms (FFA) with their matched optical coherence tomography (OCT) scans. A, Grade 1 FFA with OCT showing solitary intraretinal low-signal cystoid space in this scan plane. B, Grade 2 FFA with OCT showing low-signal cystoid spaces either side of fixation. C, Grade 3 FFA with OCT showing multiple low-signal cystoid spaces. D, Grade 4 FFA with OCT showing widespread low-signal cystoid spaces and large central cysts. (**Fig 2** *continues*.)

shown that thickening is not always present at these sites.[9] Although fluorescein leakage indicates where thickening is likely to occur in the future and where thickening, if present, is likely to be detected, it does not give a measure of thickening itself. By contrast, OCT has the potential of measuring changes in retinal thickness. However, sampling errors may theoretically lead to focal areas of thickening not being scanned. Each scan length of the Humphrey scanner is composed of 100 individual A-scans. The 3.01-mm scan length used in this study would mean an individual scan occurring every 30 μm, which would be unlikely to miss significant areas of thickening. Radial scanning protocols about a central point mean that the ends of the scan lines are separated by 1.1 mm in the case of the four scans in this study. Because uveitic CME occurs at the fovea, a scanning strategy centered on this area minimized the possibility of significant thickening remaining undetected. In this series three eyes had CME detected by FFA that was missed by OCT and all of these were grade 1. This could have been because either cystoid spaces had not yet occurred, were present but beyond the resolution of the OCT, or were missed by our scanning protocol. In all these cases it was

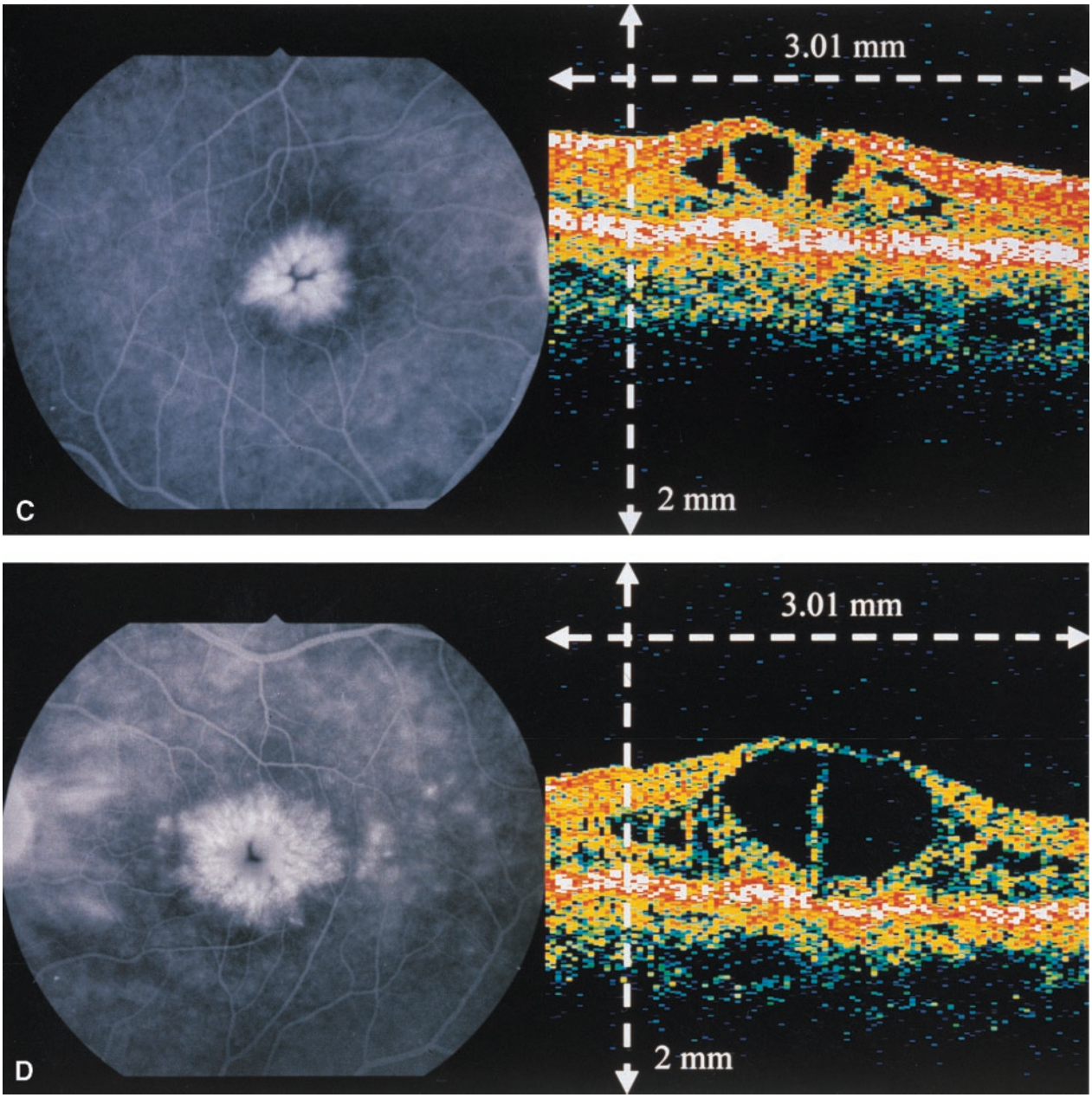

Figure 2 (*continued*).

unlikely that there was significant CME and, in practice, we now use eight radial scans centered on fixation.

In the absence of stereophotography, grading of CME on fluorescein angiograms depends on fluorescein leakage. In the presence of adequate retinal compensatory mechanisms, fluorescein leakage (grade 1) would not lead to retinal thickening or fluid space collections. This would explain the three eyes with CME grade 1 on FFA but no cystoid spaces on OCT. A transitory leak that has already ceased would not show on FFA, but a fluid space such as SRF may still be present before compensatory mechanisms have removed it. A more prolonged leak would show up on fluorescein, but this would not necessarily show the correct positioning of the fluid. Previous reports have advocated different timings for FFA. Nussenblatt et al[21] used stereopaired photographs at 3 minutes, whereas Yannuzzi et al[23,24] reported the routine use of 10-minute photographs for grading. However, they stated that no further spatial information is gained after 5 minutes. We believe that analysis of the angiograms at 3 minutes using Yannuzzi's grading is valid. It is possible, however, that some of the subretinal low reflectance spaces that were detected by OCT but not by FFA may have shown up on very late angiogram frames.

Stereophotography and stereofluorescein angiography give a degree of depth positioning, but previous authors have shown that these techniques are not useful for widespread use in uveitic patients for two reasons.[21,25] First, vitreous opacities prevent sufficiently sharp color photog-

raphy and, second, small pupils resulting from posterior synechiae prevent acceptable stereofluorescein angiography.

Attempts have been made to correlate the laminar pattern of OCT with cellular elements of histologic sections of the retina, but these require manipulation of the images.[26–28] In this study, information on the axial positioning of pathologic fluid was obtained as evidenced by the 70 eyes in which OCT could locate fluid spaces within the retina, the 15 eyes in which fluid was also located under the retina, and the 10 eyes in which fluid was only located under the retina (5 of which were missed by FFA). Although the presence of SRF in CME confirms the histopathologic studies of Wolter,[29] its clinical significance remains unclear.

Nussenblatt et al[21] found a strong correlation between macular thickening and logarithmic acuity. Their sample was a group of 10 consecutive patients that had had stereopaired photographs and therefore had sufficiently good fixation and clear media. All their patients had classical CME on FFA. Our sample consisted of a heterogeneous group of patients with uveitis and included patients with varying degrees of vitreitis and other media opacities and did not exclude patients with any degree of ischemia. In previous series of diabetic patients studied by Hee et al,[13] moderate correlation between retinal thickness measured by OCT and logarithmic acuity was found (adjusted R^2 of 0.45). However, by first correlating the retinal thickness with visual acuity, by secondly averaging the thickness values for each level of visual acuity, and by then back-correlating these averaged thickness values with visual acuity, thus reducing variation, they found good correlation (adjusted $R^2 = 0.76$ and 0.79).[13,17] Using the same approach increased our adjusted R^2 to 0.95 for cyst height and 0.93 for maximum retinal thickness. We otherwise found a weak correlation between both cyst size and retinal thickness measured on OCT and logarithmic visual acuity (adjusted $R^2 = 0.28$).

In previous studies of macular thickness in normal volunteers, OCT had an average SD of 11 μm for repeated scans of the same eyes (coefficient of variation, 7.5%).[13] Similar values were obtained in this study, in which half the eyes showed measurable cystoid spaces, SDs for macular thickness measurements being 5 to 16 μm. Measurement of intraretinal cystoid space size depends on patient fixation being maintained at the same retinal location. Because of the ellipsoid shape of intraretinal cysts, small changes in the location of the scan would lead to large changes in the height of cystoid spaces. It follows therefore that worse vision leads to worse fixation and therefore greater variation in cystoid space size. This was confirmed by the greater SD (60 μm) for repeated scans of large cystoid spaces. In contrast, the retinal thickness in the area of the cysts is less sensitive to small movements in location of the scan as was shown by the narrower SD of 16 μm for retinal thickness measurements for the same scans of large cysts. Previous investigators using OCT to follow changes in macular thickening in diabetes have measured changes in foveal height.[13] In severe CME, gross disruption of the retinal anatomy leads to difficulties in accurate location of the fovea. An alternative approach was therefore adopted in which the maximal cystoid space height was determined.

In conclusion, we have demonstrated that OCT is as effective as FFA at detecting CME in uveitic patients. It is superior in describing axial distribution of fluid, and it achieves good reproducibility.

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