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Research Note

Evidence for mild blue–yellow colour vision deficits immediately following fluorescein angiography☆

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Summary

Aims: We have investigated the short term effects of fluorescein angiography on the blue–yellow, red–green, and luminance contrast senstivity of patients with early age-related macular degeneration (ARMD).

Methods: Nine ARMD patients with no exudative complications and a visual acuity of 20/60 or better in the tested eye were selected. Cardinal colour directions for the isolation of the red–green, blue–yellow and achromatic (luminance) visual mechanisms were determined for each patient. Contrast sensitivity was measured in each cardinal colour direction immediately before and 20 min after standard 20-flash fluorescein angiography.

Results: A significant, albeit mild, reduction for blue–yellow contrast sensitivity following angiography was observed (ANOVA, α=0.05). Fluorescein angiographic exposure had no significant effect on red–green or luminance contrast sensitivity.

Conclusion: Our results show that fluorescein angiography causes at least a short term deficit selective to blue–yellow contrast sensitivity in our patient group. © 2000 The College of Optometrists. Published by Elsevier Science Ltd. All rights reserved.

Introduction

Fluorescein angiography is routinely used in the ophthalmologic examination of age-related macular degeneration (ARMD), providing essential information on retinal and choroidal vasculature. The procedure involves injection with a fluorescent dye (sodium fluorescein) followed by photography using repeated, intense bursts of short-wavelength light. Except for rare anaphylactic reactions, it is generally considered safe and without lasting side effects. Furthermore, an earlier study has shown no measurable deficits in visual acuity, luminance or colour sensitivity 48 h after angiography (Friedman *et al*., 1994). However, key visual deficits that are only apparent in the short term have not been investigated.

The potential risk of visual damage from fluorescein

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angiography in patients with ARMD does however exist (see Ham *et al*., 1980; Bloome, 1980). Firstly, the levels of light exposure lie within half a log-unit of the limit for safe exposure established by the American National Standard Institute (ANSI). As this standard is based on the exposure limit for ophthalmoscopically observable damage, functional visual deficits may occur at significantly lower exposure levels than those established by the ANSI (Mainster *et al*., 1983). Furthermore, the ANSI standard is based on measurements using continuous light exposure, and there is evidence that greater damage results from exposure to repeated light bursts such as those used in fluorescein angiography (Sperling *et al*., 1980). A third important consideration is that the occurrence of ARMD, an ailment purportedly linked to long-term light damage (Young, 1994; Taylor *et al*., 1990; Bressler *et al*., 1989), may increase susceptibility to further light damage. Evidence for this appeared in one study showing significantly longer visual recovery times for ARMD patients (8 min) than in normal patients (less than 1 min) following fluorescein angiography exposure (Collins and Brown, 1989). Finally, studies in rabbits have shown directly that the presence of intravenous sodium fluorescein increases susceptibility to retinal light damage.

In our study, we investigated the short-term effects of fluorescein angiography on visual performance on ARMD patients. In order to study these effects, we use a non-invasive technique for measuring small visual deficits following a routine fluorescein angiography test. We performed precise measurements of visual contrast sensitivity in these patients immediately before and after fluorescein angiography. Comparison between these two measurements (before and after) for each patient was the best means of establishing a reliable control condition, given the wide inter-patient variability observed in these measurements. The three colour cardinal stimuli (red–green, blue–yellow, luminance) were selected. Selective blue–yellow sensitivity deficits have been previously observed in ARMD patients under normal testing (Haegerstrom-Portnoy & Brown, 1989) and in primates following exposure to short-wavelength visible and ultraviolet light (Sperling *et al*., 1980). It is therefore conceivable that exposure to such light in fluorescein angiography may preferentially affect the already susceptible blue–yellow neural mechanism in ARMD patients. Our results on our nine ARMD patients showed no measurable losses in red–green and luminance contrast sensitivity following fluorescein angiography, but a small, yet statistically significant, blue–yellow contrast sensitivity deficit. We conclude that colour-specific measurements of contrast sensitivity provide a viable means of investigating light damage that cannot be ophthmoscopically observed.

Methods

Patients

We measured contrast sensitivity in the less affected eye of nine early ARMD patients (*Table 1*) scheduled to undergo fluorescein angiography at our clinic. Visual acuity was 20/60 or better in all tested eyes, and there were no exudative complications. The experiments were conducted in accordance with the Declaration of Helsinki on ethical testing of human subjects, and all patients gave informed, written consent prior to participating in the experiments.

Procedure

Contrast sensitivity was measured for luminance, red–green and blue–yellow cardinal stimuli immediately before fluorescein angiography (following dilation) and after angiography following a sufficient rest break (20 min). The three cardinal stimuli were selected so that each stimulus isolated one of the three postreceptoral colour mechanisms (Sankeralli and Mullen, 1997). Angiography was performed routinely by the clinical staff using a KOWA RCXV fundus camera using blue excitor and barrier filters, and consisted of exposure to 20 light flashes to each eye under test.

The contrast sensitivity measurements were performed psychophysically using stimuli generated by a Barco CCID 7651 RGB monitor driven by a Dell 333D computer (for monitor specifications and calibration details see Sankeralli and Mullen, 1997). The patient viewed the monitor at 1.5 m, and responded using a standard mouse. Patients who could not perform the task easily were excluded. The stimuli were 1 cycle per degree horizontal sinusoidal gratings (approx. $4^\circ \times 4^\circ$), which could be readily seen by the patient. The gratings were presented against a white background at 55 cd m^{-2}. A 4′ dark fixation spot was constantly presented to facilitate the patients' task. In each presentation, the grating appeared randomly in

Table 1. Clinical profiles

Patient	Age	Acuity	Phakic status	Dx (More affected eye)
1	69	20/25	Phakic	SRN[a]
2	85	20/30	Pseudophakic	Occult SRN
3	72	20/20	Phakic	Occult SRN
4	81	20/40	Phakic	Drusen
5	72	20/30	Phakic	Occult SRN
6	73	20/20	Pseudophakic	Disciform
7	85	20/25	Phakic	SRN
8	73	20/60	Phakic	Geographic atrophy
9	63	20/40	Phakic	Geographic atrophy

[a]SRN denotes sub-retinal neo-vascularisation.

one of two 500 ms intervals each signalled by a tone. The patient indicated with a mouse-button press which interval contained the grating, and audio feedback was provided.

Three colour stimuli were selected such that each uniquely activated the red–green, blue–yellow and luminance postreceptoral mechanisms. The stimuli were computed using a space based on estimates of the inputs to these mechanisms of the long-wavelength (L), medium-wavelength (M) and short-wavelength (S) cone responses (Sankeralli and Mullen, 1997). The luminance stimulus was chosen to modulate all three cone-responses to an equal proportion (it therefore appeared achromatic), and the red–green and blue–yellow stimuli were selected based on previous estimates of cone inputs to the luminance, red–green and blue–yellow neural mechanisms (Sankeralli and Mullen, 1996). Determinations of the red–green and blue–yellow cardinal colour stimuli were made for each patient individually using a minimum motion technique (Cavanagh *et al.*, 1984). In this simple procedure, a flickering (2 Hz) red–green or blue–yellow grating was titrated against a low, variable-contrast luminance grating until the point of minimum apparent flicker was selected by the patient. This precise measurement of the *isoluminant point* is based on the phenomenon that flicker is best perceived by the luminance mechanism. The isoluminant point directly yields the red–green and blue–yellow cardinal stimuli, since, at the point of minimum motion, the stimulus contains no luminance component, and is therefore detected solely on the basis of its chromatic contrast.

Contrast sensitivity was measured using a staircase procedure to determine contrast threshold (Sankeralli and Mullen, 1997). One cardinal stimulus (red–green, blue–yellow or luminance) was presented in a single run lasting between 2 and 5 min. Each run began with a presentation of a clearly visible stimulus, and each successive presentation was adjusted in contrast according to the patient's previous response: a contrast increase of 0.1 log unit followed an incorrect response, an increase of 0.05 log unit followed two consecutive correct responses. Each run produced one measurement that represented the contrast level at which the grating was correctly detected 81.6% of the time. Three measurements were made for each patient for each of the three cardinal colour stimuli. Each measurement session (before or after angiography) therefore lasted 30–45 min.

Results

Table 2 shows the deficit in contrast sensitivity for each of the three cardinal colour stimuli for each of the nine patients. We noted that the contrast sensitivities in general were all more than three times (0.5 log unit) lower than those of young, normal subjects (Sankeralli and Mullen, 1996). This result is consistent with the established deterioration of visual sensitivity with aging (Young, 1994; Werner *et al.*, 1990) and with ARMD (Haegerstrom-Portnoy, 1988; Applegate *et al.*, 1987). The average deficits for luminance, red–green and blue–yellow contrast sensitivity are represented graphically in *Figure 1*. The deficit is com-

Table 2. Luminance, red–green and blue–yellow contrast sensitivity before and after flashes[a]

	Contrast sensitivity deficit (log units)		
Patient	Luminance	Red–green	Blue–yellow
1	0.18 ± 0.05	-0.14 ± 0.12	-0.10 ± 0.10
2[b]	0.13 ± 0.11	-0.21 ± 0.10	0.01 ± 0.16
3	-0.20 ± 0.17	0.05 ± 0.07	-0.12 ± 0.07
4	-0.06 ± 0.21	0.09 ± 0.17	0.06 ± 0.10
5	-0.15 ± 0.10	0.00 ± 0.04	0.21 ± 0.05
6[b]	0.24 ± 0.14	0.16 ± 0.18	0.35 ± 0.16
7	0.01 ± 0.06	0.08 ± 0.09	0.14 ± 0.07
8	0.14 ± 0.11	0.05 ± 0.08	0.14 ± 0.03
9	0.06 ± 0.24	0.09 ± 0.27	-0.01 ± 0.28
Average	0.04 ± 0.05	0.02 ± 0.04	0.08 ± 0.05

[a]Deficit is the difference between contrast sensitivity before and after fluorescein angiography. A positive deficit signifies deteriorated performance following angiography. The error measure for each patient represents the standard error of the three measurements for stimulus, while that of the average deficit is the standard error of the patient population ($n = 9$).
[b]Denotes pseudophakic patient.

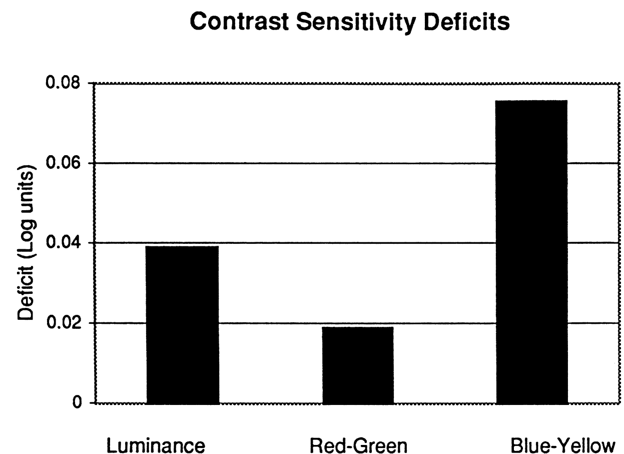

Figure 1. Average contrast sensitivity deficits following fluorescein angiography. The bar chart shows the mean deficit across patients for luminance, red–green and blue–yellow contrast sensitivity. The standard error of these deficits across patients ($n = 9$) was approximately 0.05 (Table 2). Two-way ANOVA and Walsh tests reveal that the blue–yellow deficit was statistically significant ($\alpha = 0.05$).

puted as the difference in log units between contrast sensitivity before and after fluorescein angiography: a positive deficit implies a lower contrast sensitivity following angiography. The mean deficits across patients were found to be 0.04 log units (9%) for luminance, 0.02 log units (5%) for red–green, and 0.08 log units (17%) for blue–yellow. Thus, on average, the blue–yellow deficits were found to be higher than for luminance and red–green. More importantly from a clinical viewpoint, four patients out of the nine exhibited blue–yellow deficits that were statistically significant (two standard errors or greater). This compares with one patient showing luminance deficits and none showing red–green deficits.

As a population, the deficits in blue–yellow contrast sensitivity were found to be statistically significant, as obtained from a two-way repeated-measures ANOVA test ($\alpha = 0.05$). On the other hand, the deficits in red–green and luminance contrast sensitivity were not significant (power < 0.15). These results were confirmed by the results of a Walsh test ($\alpha = 0.05$) that relaxes the normality assumption on the data (Siegel, 1956). To test whether the blue–yellow deficits reflect an overall deterioration in performance for each patient after angiography (e.g., due to fatigue), we correlated these deficits with those for luminance. We obtained a correlation coefficient of 0.27, well below the critical value of 0.60 at the 5% significance level. We therefore conclude that the blue–yellow deficit arises from a cause that is independent of overall patient performance.

Discussion

We observe that blue–yellow contrast sensitivity exhibits a significant deterioration following fluorescein angiography. This is a new finding, and conflicts with a recent study showing an absence of such deficits (Friedman *et al*., 1994). This discrepancy has several possible causes. Friedman *et al*. studied patients with assorted visual ailments including only three with ARMD. Our study may therefore reveal an effect specific to ARMD patients, consistent with hypothesised links between ARMD and light damage. Secondly, Friedman *et al*. used less sensitive techniques for evaluating red–green and blue–yellow deficits (D-15 colour test and two-color increment thresholds). As these tests were designed to investigate much larger colour deficits (as arise for example from congenital colour blindness), it is conceivable that our technique reveals deficits that these other techniques do not. A third important consideration is that Friedman *et al*. tested for deficits at much longer (48 h) after angiography than ours. It is entirely conceivable that the visual losses observed in our study are only temporary. However, we do not have the ethical means of testing our patients over a prolonged period to confirm this hypothesis.

At the same time, the short onset of our observed blue–yellow deficits has important consequences. Specifically, these visual deficits occur well before the time of constant exposure (48 h) required to inflict ophthalmoscopically observable damage (Ham *et al*., 1980). This occurrence of visual deficits is also consistent with occasional subjective reports to one of the authors (JCC) of prolonged visual impairment following angiography. Our findings indicate that visual deficits may occur earlier, and at lower levels of light exposure, than observable tissue damage. At the same time, our observed effects cannot be linked to fleeting visual deficits, such as dazzle recovery and transient tritanopia, which disappear well before the time of our testing after angiography (Collins and Brown, 1989; Haegerstrom-Portnoy and Verdon, 1991; Wisowaty, 1983; Mollon and Polden, 1979).

The specificity of contrast deficits to blue–yellow sensitivity indicates possible sites for the occurrence of these deficits. The first site is that of S cones, which only has inputs to the blue–yellow neural mechanism and not to luminance and red–green (see Sankeralli and Mullen, 1996). This hypothesis is supported by earlier evidence of the susceptibility of S cones to phototoxic damage by short-wavelength visible light (Sperling *et al*., 1980). Alternatively, phototoxic damage may arise in the blue–yellow neural mechanism that arises from combination of cone signals in the early stages of retinal processing. In addition, it is still an open question what the causes of the blue–yellow sensitivity deficits are. The deficits may be caused by exposure to bright flashes or by the presence of the fluorescent dye. One study in rabbits (Hochheimer *et al*., 1987) suggests that it is combination of these two effects that is responsible for visual dysfunction. Mechanisms for the interaction between the phototoxic effects of the bright short-wavelength flashes and the chemotoxic effects of the dye have been proposed (Hochheimer *et al*., 1987; Gottsch *et al*., 1990).

There are still several questions that require a much larger patient sample to resolve. Firstly, it is still an open question whether our results are specific to ARMD patients, although a comparison with the results of Friedman *et al*. (1994) and the link between light damage and ARMD suggest that such specificity is plausible. Secondly, it would be useful to track the progress of these visual deficits with that of ARMD. In our study, for instance, we observed that the patient with the most severe case of ARMD (♯6) also exhibited the largest deficit. Finally, a large volume of testing is required to ascertain whether our observed deficits in blue–yellow sensitivity disappear after a sufficient recovery time. Nonetheless, our results identify

a potential hazard in routine ophthalmological tests using fluorescein angiography, and point to a possible means of investigating these risks further.

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