Critical flicker fusion test of potential vision

Hema Shankar, BMBS, MA, Konrad Pesudovs, PhD

PURPOSE: To continue developing a potential vision test based on the critical flicker fusion (CFF) phenomenon by using a brighter stimulus and optimizing its size.

SETTING: Flinders Eye Centre, Flinders Medical Centre, Flinders University, Bedford Park, South Australia, Australia.

METHODS: In a prospective nonrandomized study, 225 participants were assigned to 1 of 4 groups: normal, media opacity only, retinal/neural disease only, and cataract plus retinal/neural disease. Participants were recruited if they were 20 years or older but were excluded if they had a neurological disorder or medication known to affect CFF. The CFF thresholds were measured for 3 stimulus sizes: 0.5 degree, 1.0 degree, and 1.5 degrees. Discrimination between groups was tested by analysis of variance and receiver operating characteristic analysis. The relationship between visual acuity and CFF in eyes without media opacity was determined by linear regression and used to predict visual outcomes in 23 eyes having cataract surgery.

RESULTS: The mean age of the 225 participants was 71.4 years \pm 13.2 (SD); 134 (59.8%) were women. The normal group had 41 participants, and the other 3 groups had 61 participants each. Critical flicker fusion thresholds were reduced in retinal/neural disease but resistant to image degradation from media opacity. The 1.5-degree stimulus had 88% sensitivity and 90% specificity for discriminating groups. Visual acuity after cataract surgery was accurately predicted within \pm 1 line in 43% of eyes, \pm 2 lines in 83%, and \pm 3 lines in 100%. All eyes with poor visual acuity (>0.50 logMAR) or dense cataract (>4.0 Lens Opacities Classification System III) were predicted within \pm 2 lines.

CONCLUSIONS: The CFF phenomenon effectively discriminated between subjects with and without retinal/neural disease and accurately predicted visual outcome after cataract surgery. The use of a brighter stimulus enhanced performance in cases of dense media opacity.

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Cataract surgery has been established as a relatively safe and effective procedure.^{1,2} More than 95% who have the surgery achieve a visual acuity of 20/40 or better if there is no comorbid disease.³ However, in patients with comorbid disease, particularly age-related macular degeneration (ARMD), cataract surgery may result in poor visual outcomes and subsequent patient disappointment.⁴ Indeed, the benefits of cataract surgery to patients with ARMD are open to debate.^{4–9} Whether to recommend surgery in these patients can pose an important clinical dilemma as it is difficult to determine the relative contribution of each pathological process to the patient's existing visual disability. Potential vision tests can be a valuable aid in this decision-making process if they can accurately predict visual function behind cataract and other media opacity. The usefulness of existing potential vision tests in predicting visual acuity when preoperative acuity is 20/200 or worse has been discredited in a major review by the Agency for Health Care Policy and Research.¹⁰ Therefore, there is

a need to develop a test of potential vision that can predict visual outcomes in eyes with very dense cataract or other media opacity where the extent of the media opacity interferes with the clinician's ability to gauge the benefit of cataract surgery in improving the patient's postoperative visual outcomes.

It has been known for more than 100 years that posterior segment eye disease can impair critical flicker fusion (CFF) frequency.^{11–16} Recently, the CFF phenomenon has been suggested as a test of potential vision able to penetrate dense cataracts.^{17–19} This is because CFF has been shown to be unaffected by the presence of cataract and other media opacities^{20–22} as long as a bright stimulus is used^{14,23}; yet, it is sensitive to retinal and optic nerve disease.^{12,14–16} Moreover, as CFF reduction from retinal/neural disease correlates reasonably with visual acuity, it can be used to predict postoperative visual acuity.

Critical flicker fusion is known to be affected by several factors including target luminance, target color, and target

size.²⁴ We incorporated these factors into the design of a testing device. Working on the hypothesis that an even brighter stimulus may better penetrate dense cataract, we incorporated a brighter light-emitting diode (LED) that recently became available to double the stimulus luminance. Taking the lead from previous work,^{18,25} we selected a red stimulus to minimize the effect of short-wavelength absorption from the aging crystalline lens and nuclear cataract. One problem with CFF as a potential vision test, identified by Vianya-Estopà et al.,¹⁹ is that testing with a 1.5-degree target is limited in sensitivity to macular holes and early ARMD. This is probably because foveal defects could be masked by surrounding healthy retina. Theoretically, a smaller target measures foveal vision specifically and may detect these small macular lesions. On the other hand, smaller targets give rise to lower CFF thresholds,²⁶⁻²⁸ which truncates the range of CFF scores and hampers the differentiation of normal from abnormal eyes.¹⁸ This may be partially offset by using a brighter stimulus to increase CFF.

Therefore, we chose to repeat the experiment conducted by Vianya-Estopà et al.¹⁸ and test 3 small targets giving visual angles of 0.5 degree, 1.0 degree, and 1.5 degrees. The aims of this study were to determine the smallest (1000 cd/m²) stimulus that gave good discrimination between eyes with normal posterior segments and eyes with abnormal posterior segments and to test our hypothesis that a brighter target would penetrate dense cataracts more effectively and optimize the efficacy of a smaller target. To use CFF as a potential vision test, the relationship between CFF threshold and visual acuity in eyes without media opacity was quantified for each of the 3 stimulus sizes and used to predict visual acuity. The ability of CFF to predict visual acuity behind cataract was tested in a series of eyes having cataract surgery, and an attempt was made to quantify the repeatability of CFF thresholds.

Dr. Russell Phillips, Dr. Richard Mills, Dr. John Pater, Associate Professor Jamie Craig, and Professor Douglas Coster facilitated access to clinical patients.

Corresponding author: Konrad Pesudovs, NH&MRC Centre for Clinical Eye Research, Department of Ophthalmology, Flinders Medical Centre, Bedford Park, South Australia, 5042, Australia. E-mail: konrad.pesudovs@flinders.edu.au.

SUBJECTS AND METHODS

Participants

Participants were recruited from the Eye Clinic at Flinders Medical Centre, Bedford Park, South Australia, Australia. The study gained approval from the Flinders Clinical Research Ethics Committee and followed the Declaration of Helsinki for research involving human participants. Inclusion criteria varied by clinical population (see below), and patients 20 years or older were selected. Exclusion criteria included neurological disease or medication known to affect CFF as well as physical or language impediments to participating in the testing. Neurological disorders known to impair CFF include epilepsy,²⁹ multiple sclerosis,³⁰ Parkinson's disease,³¹ Alzheimer's disease,³² dementia, alcoholism,³³ and cognitive impairment.³⁴ Medications known to affect CFF include antihistamines,^{55,36} tricyclic antidepressants,³⁷ benzodiazepines,³⁸ antiepileptics,²⁹ barbiturates,³⁹ and other sedatives.⁴⁰ The inability to understand English sufficiently to follow testing instructions, insufficient mental ability to perform the tests, inability to see any of the 3 target sizes, and physical disability that made it arduous to perform the tests (eg, wheelchair use) precluded patients from being recruited for testing. Patients in whom both eyes satisfied the inclusion and exclusion criteria had both eyes included in the analyses.

Four groups were studied. The normal control group had no eye disease and visual acuity better than 0.2 logMAR (\sim 20/30 Snellen). A second group had retinal/neural disease only (no cataract or other media opacity). A third group had media opacity only (no retinal/neural disease), and a fourth group had cataract and retinal/neural disease. Included in the retinal/neural disease groups were patients with macular, optic nerve, and visual pathways lesions. The rationale for this is that a potential vision test should be able to detect reduced visual potential regardless of the level at which the lesion occurs.

Critical Flicker Fusion Test Procedure

The CFF test apparatus was built by Flinders Biomedical Engineering at Flinders Medical Centre. The stimulus consisted of a red Luxeon Star 1 W LED (Phillips Lumileds Lighting Co.) with collimating optics of nominal luminous flux of 44 lumens, a dominant wavelength of 625 nm (range 620.5 to 645.0 nm, bandwidth 20 nm [spectral width at 1/2 peak intensity]), and capability of emitting a frequency up to 110 Hz. The circular stimulus was 8.0 mm in diameter and subtended visual angles of 0.5 degree, 1.0 degree, and 1.5 degrees at viewing distances of 91.7 cm, 45.8 cm and 30.5 cm, respectively. The mean measured LED luminance was 1000 cd/m^2 , and the mean luminance of the surrounding screen was 160 cd/m². This intensity of the stimulus is demonstrably safe to the retina, and there is no risk for inducing an epileptic seizure from a small (0.5- to 1.5-degree) target with a 2-second duration.⁴¹ The stimulus was driven with a 350 mA current source, with the pulse width modulated to produce a sine wave with a modulation depth of 95%. The LED source was mounted at the center of a matte white 20 cm² rectangular screen (Figure 1). The stimulus could be presented continuously or as a 2-second pulse. The CFF test apparatus was calibrated and metered in steps of 0.1 Hz. The LED flashing rate was measured by the integral crystal controlled frequency counter based on a common microcontroller. The basic accuracy of this counter was quoted as "20 parts per million," but the display resolution of 0.1 Hz was the limiting factor. During the design phase, accuracy

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From the NH&MRC Centre for Clinical Eye Research, Department of Ophthalmology, Flinders Medical Centre, and Flinders University of South Australia, Bedford Park, Australia.

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Figure 1. The CFF testing apparatus.

was repeatedly confirmed using the frequency-counting function of a Tektronix TDS 1002 digital storage oscilloscope.

Measurements were taken monocularly with any refractive error, including presbyopia, corrected. Although it has been shown that the CFF threshold is minimally affected by pupil dilation,⁴² for consistency all testing was performed with natural pupils. The participant was instructed to look directly at the center of the red light. Care was taken with instruction and observation to ensure the participant did not use eccentric fixation. Several stimuli were presented initially to orient the participant to the sensation of flicker (10 to 20 Hz) and fusion (55 to 65 Hz) before test measurements were recorded. Two-second pulse stimuli were used to prevent adaptation and therefore alteration of the CFF threshold.^{24,43,44} The threshold was determined using a staircase paradigm with 5 ascending and 5 descending presentations in 1 Hz steps. A fusion threshold was recorded for each ascending run (lowest frequency stimulus to appear steady), and a flicker threshold was recorded for the descending run (highest frequency stimulus to appear to flicker). The mean of the 10 recordings was calculated as the CFF threshold. The procedure was performed for the 3 stimuli sizes in random order. The CFF testing took approximately 15 minutes, which research has shown does not cause problems with fatigue.²⁸

Before CFF testing, participants were refracted and visual acuity was measured using Early Treatment Diabetic Retinopathy Study logMAR charts at 4 m with a mean luminance of 160 cd/m² using by-letter scoring.⁴⁵ After testing, pupils were dilated and participants had a full ophthalmologic examination to establish the diagnoses, including Lens Opacities Classification III (LOCS III) grading of cataract.⁴⁶

Statistical Analysis

The groups were compared by analysis of variance with post hoc (Sheffé) testing for age, visual acuity, and CFF. The relationship between visual acuity and CFF was explored using linear regression. This relationship was used to predict visual acuity from CFF in preoperative cataract patients. The success of this prediction was tested using descriptive statistics. These statistical analyses were performed using SPSS (version 12.0.1, SPSS, Inc.). The optimum target size for differentiation between the media opacity and the retinal/neural disease groups was determined by receiver operating characteristic (ROC) analysis using Analyse-it software (version 1.71, Analyse-it Software, Ltd.).

The within-participant repeatability of the CFF threshold was evaluated for each target size by comparing the 5 ascending and 5 descending measures during each measurement. Repeatability was assessed in terms of the coefficient of repeatability, which is obtained by calculating the standard deviation of the difference between the repeated measures and multiplying this by 1.96.⁴⁷ This represents the 95% confidence interval (CI) for any discrepancy between test and retest data. This analysis was conducted in Microsoft Excel 2003.

RESULTS

The mean age of the 225 participants was 71.4 years \pm 13.2 (SD); 134 (59.8%) were women. A patient with macular degeneration was excluded for being unable to see any of the 3 CFF targets (visual acuity worse than 1.60 log-MAR [Snellen 20/800]). Two other participants with macular degeneration (visual acuity 20/250 and 20/400) could not see the 0.5-degree target but could see the 2 larger targets; their data were included in the analyses.

There were 41 participants in the normal control group and 61 participants each in the media opacity only, retinal/ neural disease only, and media opacity and retinal/neural disease groups. The media opacity only group comprised 59 cases with cataract and 2 with posterior capsule opacification. The retinal/neural disease only group comprised 31 cases with ARMD, 9 with diabetic maculopathy, 7 with diabetic retinopathy, 4 with glaucoma, 3 with cystoid macular edema (CME), 2 with vascular occlusions, 2 with visual pathways lesions, and 1 each with retinal detachment, amblyopia, and macular hole. The group with media opacity and retinal/neural disease included 2 cases with corneal disease and 59 with cataract. It also included 26 cases of ARMD, 15 of glaucoma, 4 with visual pathways lesions, 3 with epiretinal membranes, 2 with diabetic maculopathy, and 1 each with diabetic retinopathy, retinal detachment, amblyopia, vascular occlusion, and CME; 6 participants had multiple conditions.

The normal group had a mean age of 55.4 \pm 16.9 years), which was significantly younger than the mean age in the 3 disease groups (F_(3,220) = 38.8; *P*<.001). The 3 disease groups were similar in age (*P*>.05, Sheffé post hoc); the mean age was 74.3 \pm 6.7 years in the media opacity only group, 73.1 \pm 11.3 years in the retinal/neural disease only group, and 77.6 \pm 7.8 years in the media opacity and retinal/neural disease group. Similarly, there was no significant difference in visual acuity between the media opacity only group (mean 0.27 \pm 0.30 logMAR; Snellen 20/37), retinal/neural disease only group (mean 0.36 \pm 0.45

logMAR; Snellen 20/46), or media opacity and retinal/ neural disease group (mean 0.39 \pm 0.32 logMAR; Snellen 20/49) (*P*>.05, Sheffé post hoc). However, the normal group had significantly better acuity (mean -0.07 ± 0.08 logMAR; Snellen 20/17) (F_(3,220) = 19.63; *P*<.001).

Figure 2 shows the CFF thresholds by group. For each target size, there were significant differences between groups: 0.5-degree target ($F_{(3,163)} = 23.21$; *P*<.001), 1.0-degree target ($F_{(3,217)} = 31.06$; *P*<.001), and 1.5-degree target ($F_{(3,165)} = 31.86$; *P*<.001). Post hoc analysis

indicated no significant differences in the CFF thresholds between the normal group and the media opacity only group for any of the 3 target sizes (P>.05). However, significant differences existed between both the normal group and the media opacity only group and the retinal/neural disease with or without media opacity groups for all target sizes (all P<.001). Therefore, retinal/neural disease affected CFF, but media opacity did not.

Linear regression analysis of the relationship between CFF and visual acuity in the group without media opacity



showed a significant relationship (P < .001) for all 3 target sizes, which are given as the equation and coefficients of determination (r^2): (visual acuity = 1.503 - 0.040CFF_{0.5°}; 0.50), (visual acuity = 1.901 - 0.047CFF_{1.0°}; 0.54), and (visual acuity = 2.217 - 0.053CFF_{1.5°}; 0.61) (Figure 3).

The ROC curves, plotted for the 3 target sizes and for visual acuity are shown in Figure 4. This analysis identified the cutoff point for best discrimination between the 2 groups. The proportion of CFF values below the cut-off value among the retinal/neural disease participants represents sensitivity (proportion of true positives), and the proportion of CFF values above the cutoff value among the media opacity group represents specificity (proportion of true negatives). The point closest to the upper left-hand corner of the graph represents the highest sensitivity and specificity and therefore is the best criterion to differentiate between retinal/neural disease and media opacity participants. Figure 4 suggests that 1.5 degrees best discriminates between retinal/neural disease and media opacity cases as this target size gave the point of highest sensitivity





Figure 4. The ROC curves plotting sensitivity versus specificity in 61 participants with media opacity and 61 participants with retinal/neural disease for CFF thresholds at 3 target sizes (*A*) and visual acuity (*B*).

(88.1%) and specificity (90.0%), which was at 40.5 Hz. The relative discriminative ability of the 3 target sizes can be quantified using the area under the curve (AUC) for each target size. The AUC was 0.93 for the 1.5-degree target (95% CI, 0.88-0.98), 0.94 (95% CI, 0.89-0.98) for the 1.0-degree target, and 0.89 (95% CI, 0.83-0.96) for the 0.5-degree target. All target sizes were statistically significantly different from random level performance (AUC 0.50) and visual acuity (AUC 0.55; 95% CI, 0.44-0.65) (Figure 4, *B*). Pairwise comparisons showed that the 0.5-degree target size curve had significantly less AUC than the 1.5-degree target size curve (P<.05) but that the 1.0-degree target was indistinguishable from the other target sizes.

The coefficient of repeatability across all participants was ± 1.9 Hz for the 0.5-degree target, ± 1.9 Hz for the 1.0-degree target, and ± 2.1 Hz for the 1.5-degree target. The coefficient of repeatability was better for normal participants (0.5 degrees, 1.0 degrees, 1.5 degrees: ± 1.5 , ± 1.6 , and ± 1.6 , respectively) and media opacity only participants (± 1.9 , ± 1.7 , and ± 1.8 , respectively) and poorer for participants with retinal/neural disease (± 2.2 , ± 2.1 , and ± 2.4 , respectively).

The group having cataract surgery comprised 23 eyes of 21 patients (14 women) with a mean age of 74.8 \pm 9.7 years (range 51 to 90 years). The mean visual acuity was $0.35 + 0.22 \log MAR$ (range 0.10 to 0.80 logMAR). The mean LOCS III cataract grades were NO 3.5 \pm 0.8 (range 2.2 to 5.0), NC 3.5 \pm 1.0 (range 2.2 to 6.0), C 2.7 \pm 0.8 (range 1.0 to 4.5), and P 1.5 \pm 1.1 (range 0.1 to 3.6). Twelve patients had cataract alone, and the others had cataract and comorbidity: 7 had ARMD, 3 had glaucoma, and 1 had ARMD and a stroke. The mean postoperative visual acuity was 0.10 ± 0.14 logMAR (range -0.16 to 0.42 log-MAR) and was predicted from CFF to be 0.07 \pm 0.18 log-MAR (range -0.22 to 0.59 logMAR). Postoperative visual acuity was correctly predicted within ± 1 line in 10 cases (43%) and within ± 2 lines in 19 cases (83%); all cases were predicted to within ± 3 lines. None of the 4 eyes that were not predicted within ± 2 lines of visual acuity had particularly dense cataract, and only 1 had comorbidity. All 6 eyes with poor visual acuity (0.50 logMAR or worse) and all 8 eyes with dense cataract (any individual LOCS III grade 4.0 or greater) were correctly predicted within ± 2 lines of visual acuity.

DISCUSSION

The results in this study confirm the findings in several previous studies of the use of CFF as a potential vision test.^{17–19} The CFF thresholds were highly repeatable,¹⁸ with 95% of cases varying by fewer than ± 2 Hz, with slightly better performance in normal eyes and slightly worse performance in eyes with retinal/neural disease. Critical flicker fusion frequency thresholds are resistant to image degradation caused by cataract and other media opacities^{14,17–19}; there was no significant reduction in CFF thresholds for any of the 3 target sizes in the media opacity group compared with the normal group, despite visual acuity being much worse in the media opacity group (Figure 2). The results also confirm that CFF thresholds are lower in the presence of retinal/neural disease (Figure 2).^{11,14–19} Therefore, it is safe to assume that in the presence of cataract and retinal/neural disease, any reduction in CFF is due to the latter, and this has implications for poor visual outcomes postoperatively.

All 3 target sizes discriminated well between the media opacity and retinal/neural disease, as shown by the ROC analysis (Figure 4). The 1.0-degree and 1.5-degree targets performed similarly based on the AUC analysis (0.94 and 0.93, respectively), but the point of optimal discrimination was closer to ideal for the 1.5-degree target. However, the 0.5-degree target performed significantly worse than both larger targets (AUC 0.89). This may, in part, be related to

the lower CFF results found with decreased target size in all groups, which compresses the range of scores and thus reduces discrimination. Based on these results, 1.0-degree or 1.5-degree targets would be the sizes of choice for potential vision testing. Vianya-Estopà et al.¹⁸ found that a 1.5-degree target (AUC 0.79) discriminated better than a 1.0-degree target (AUC 0.75) or a 0.5-degree target (AUC 0.70). The main difference between the 2 studies is that the we used a brighter stimulus (1000 cd/m² versus 500 cd/m²). Vianya-Estopà et al. found lower CFF thresholds as a result of the lower luminance in the normal eye and media opacity groups as follows: 0.5 degrees, 1.0 degrees, and 1.5 degrees had 24 Hz, 28 Hz, and 30 Hz thresholds, respectively. This suggests, as hypothesized, that a brighter stimulus enhances performance because of better penetration of media opacities and the higher CFF thresholds better separate the data in each group.

The linear regression of CFF against visual acuity in eyes without media opacity showed a strong relationship, especially at 1.5 degrees ($r^2 = 0.61$), which is markedly better than that found by Vianya-Estopà et al.¹⁸ (1.5 degrees; $r^2 = 0.36$) or Bueno del Romo et al.¹⁷ (1.5 degrees; $r^2 = 0.43$). This relationship was used to predict visual acuity from CFF in eyes with media opacity. However, the graphs in Figure 3 show significant variance around the mean. This suggests that the ability of CFF to predict visual acuity should be considered as fairly coarse. Therefore, CFF as a potential vision test may not be very useful in cases of mild cataracts with good preoperative visual acuity, nor is it really necessary because traditional ophthalmic judgment can perform well in such cases.¹⁷ The usefulness of this test lies in the strength of the visual acuity-CFF correlation extending to eyes with very dense media opacity and poor preoperative vision, which allows for accurate and effective prediction of visual outcome in these eyes, which is difficult to predict by clinical judgment alone.¹⁷ Indeed, this study established the usefulness of CFF as a potential vision test; all eyes were correctly predicted within \pm 3 lines of visual acuity and 83%, within \pm 2 lines of visual acuity. All eyes with poor visual acuity ($>0.50 \log MAR$) or dense cataract (>4.0 LOCS III) were accurately predicted within ± 2 lines of visual acuity.

The prediction of visual outcomes of cataract surgery in our study compares favorably with results in previous studies comparing potential vision tests.^{17,19} The classic potential vision tests—the potential acuity meter (PAM) and laser interferometry—struggle to penetrate cataracts, even at levels that only degrade visual acuity to 6/12.¹⁹ Superilluminated pinhole, PAM, and laser interferometry were all shown to be ineffective in the presence of dense cataract.^{17,19} These 3 tests also tend to overestimate visual acuity in macular disease.¹⁹ Bueno del Romo et al.¹⁷ compared ophthalmic judgment in predicting postoperative visual acuity with potential vision tests (including CFF). They found that CFF performed the best of all the potential vision tests in cases of dense cataract (67% within ± 2 lines and 80% within ± 3 lines). In contrast, ophthalmic judgment predicted 53% within ± 2 lines and 60% within ± 3 lines; the PAM and superilluminated pinhole predicted 27% and 40%, respectively. With our CFF arrangement, the results were even better. The main limitation of CFF as a potential vision test, identified by Bueno del Romo et al.¹⁷ and Vianya-Estopà et al.,¹⁹ is an occasional failure to be sensitive to visual acuity loss from macular disease, particularly compared to the superilluminated pinhole test (in mild to moderate cataract). Both these studies used the CFF testing model from the earlier pilot study by Vianya-Estopà et al.¹⁸

The current study addressed some perceived shortcomings of the earlier model by increasing target luminance. We established both 1.5 degrees and 1.0 degree to be ideal targets with improved performance compared with that in the earlier studies. It is possible that the use of a smaller, brighter target will improve the sensitivity of CFF to macular disease, and this will be tested more extensively with our next prototype. Another potential source of error in macular disease is subtle eccentric fixation during testing as this would elevate CFF. Therefore, we intend to include more sophisticated fixation monitoring in our next prototype.

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