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Review

The theory of critical flicker fusion frequency and its application in cataracts

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ABSTRACT

Background: Due to media opacity, it is usually difficult to accurately evaluate the postoperative visual acuity in cataracts patients. As a small and portable tool, the critical flicker fusion frequency (CFF) device reflects the temporal resolution of visual function and has been widely used in clinical research. However, poor understanding of the technique and equipment limitations have restricted its clinical application in China.

Main text: There was a decrease in the CFF value in various ophthalmic diseases, indicating that the CFF is sensitive to detect visual functional changes. A number of studies have shown that the CFF test can accurately distinguish patients with simple cataracts from those with cataracts combined with fundus disease, and, as a visual test, it can more accurately predict postoperative visual acuity without being affected by media opacity. This study comprehensive reviews the basic principles of CFF and its application in ophthalmology, especially in cataracts.

Conclusions: As one of the tools for dynamic visual function detection, the CFF test could help doctors to assess the possible presence of fundus disease in cataracts patients, especially in eyes with dense cataracts, and more precisely provide a reasonable visual prognosis than other available visual tests.

From a neurophysiological perspective, the mammalian visual system generally consists of at least two major pathways, namely the magnocellular pathway and parvocellular pathway, which reflect the temporal and spatial resolution, transmitting signals individually and in parallel. The visual information transmission process can be briefly described as follows: The optical signal handled by cone cells and rod cells is converted into an electrical signal at the retina and then passes through bipolar cells to retinal ganglion cells. Then, the axons of ganglion cells extend to the optic tract and exchange signals with neurons at the lateral geniculate nucleus. Subsequently, axons project *via* the optic radiation and eventually transmit to the visual cortex in the occipital lobes, temporal lobes, and other higher cortical areas. This is the direct pathway to the primary visual cortex,[1,2] which centralizes information processing about static perception, depth perception, and motor perception. The lateral geniculate nucleus is composed of three types of cells: the magnocellular cells in the inner two magnocellular layers (1 and 2), the parvocellular cells in the outer four parvocellular layers (3, 4, 5, and 6), and koniocellular cells in the koniocellular layers ventral to each of the magnocellular and parvocellular layers. Among them, the magnocellular pathway carries information about large, fast things (low spatial frequency, high temporal frequency). In contrast, the parvocellular pathway carries information about small, slow, colorful things (high spatial frequency, low temporal frequency).[2–4] These two pathways are relatively independent and would transmit overlapping messages only in certain circumstances.[5] The neural efficiency of the magnocellular pathway depends on the neuron recovery time after visual stimulation.[6] Animal research has shown that magnocellular cells have a shorter neuronal refractory period and can perceive high temporal frequency compared to parvocellular cells.[2,3]

As a sensitive indicator of temporal resolution, the critical flicker fusion frequency (CFF) is defined as the frequency at which a flickering light is perceived as a stable and continuous light.[7] The CFF test has been widely used in various ophthalmic diseases, including glaucoma, age-related macular degeneration (AMD), amblyopia, retinal diseases, and optic nerve diseases. In addition, the CFF test has been used as a potential visual

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test (PVT) to assess visual function and predict postoperative visual acuity for cataract patients. Our article comprehensively reviews the principles of CFF and its current application in cataracts.

1. Ferry-Porter law

The Ferry-Porter law states that the CFF value has a linear relation with the logarithmic light luminance.[8,9] The slope of the line is affected by retinal eccentricity, target size, light wavelength, and background luminance.[10–12] Granit et al. found that the CFF value has a linear relationship with the logarithm of the area of retinal stimulation,[13] which correlated to the number of stimulated ganglion cells.[14] Therefore, a larger flicker target could have a higher CFF value, so the flicker size should be limited to a 2°visual angle. Also, since the transmission speed of photoreceptors in the peripheral retina is faster than that of the central area, a higher CFF value is found in the peripheral retina within 50°retinal eccentricity.[14] Hamer et al. found a steeper slope of the Ferry-Porter equation when the flicker light was at 552 nm wavelength than that at 642 nm, which may be attributed to faster signal transmission in the M-cone pathway than that in the L-cone pathway.[10]

2. Factors influencing the CFF

The CFF value is affected by confounding factors of physiology, pathology, and pharmacology. It decreases with age, and younger people have a higher CFF value than older people[12,15,16] as aging is associated with decreased prefrontal cortex function resulting in poor CFF performance.[17] Moreover, the CFF value is highly associated with cortical arousal and serves as a measurement of cognitive performance.[18,19] Breathing 100% oxygen can enhance neural stimulation, thus, increasing brain blood flow and improving cerebral performance.[20,21] Health volunteers obtained improved CFF values by breathing pure normobaric oxygen for 10 min, but showed the inverse result in hypoxia conditions.[22,23] The CFF test has been widely used in diving field studies, especially in evaluating divers' cognitive functions regarding nitrogen narcosis and high-pressure nervous syndrome (HPNS).[22,24] An improvement in the CFF value was observed in professional divers inhaling hyperbaric oxygen (PPO2 of 2.8 ATA), having better attention and alertness as a result of enhanced neuronal excitability.[25] Another study showed that divers had decreased CFF value after diving under a depth of 610 m using a helium-oxygen mixture (PO2:0.38–0.52 ATA), simulating cerebral function declined caused by HPNS, and the CFF value variations were closely parallel to electroencephalogram (EEG) modifications.[26] In addition, the CFF value is affected by the mental state, and decreased in a central fatigue state,[27] but not in a peripheral fatigue state, and may mildly increase after aerobic exercise.[28] Both central nervous system stimulants and depressants affect the CFF value. For example, psychostimulants (*e.g.*, amphetamine sulfate)[29] and selective serotonin reuptake inhibitors (SSRIs; *e.g.*, citalopram, fluoxetine, and sertraline) positively affect the CFF value.[30] In contrast, sedative-hypnotic drugs, anxiolytics, antidepressants, and small doses of alcohol can reduce the CFF value.[31,32] Besides their primary effects, they have an additional impact on CFF measurements by altering the pupil size.[33,34] Mydriasis can transiently improve the CFF value.[35] Also, the CFF value could add to an average of 3.2 Hz after pupillary dilation with 1% tropicamide and 2.5% phenylephrine compared with the physiological state in healthy subjects.[36] Recent studies have shown that the concentrations of lutein and zeaxanthin in the macula positively correlated with the CFF value, indicating that daily vitamin supplementation may help to improve visual function.[37]

3. CFF application in ophthalmology

Poor performance in the CFF test generally occurs in many ocular diseases, including glaucoma, diabetic retinopathy (DR), AMD, and ischemic optic neuropathy or demyelinating optic neuritis, which can lead to varying degrees of decline in CFF value. However, no significant difference in the CFF value was found in patients with amblyopia due to congenital cataracts.[38] Yoshiyama suggested that the CFF test could distinguish glaucoma patients from healthy subjects and detect early visual field defects.[39] Lecleire-Collet et al. found that early neurological dysfunctions could be detectable by the CFF test prior to visible characteristic DR fundus changes.[40] Maier et al. reported a significant reduction in the CFF value both in dry or wet AMD patients with a better sensitivity of 14-Hz.[41,42] Fu et al. found a decreased CFF value in patients with demyelinating optic neuritis and ischemic optic neuropathy. The CFF performance is highly correlated with other visual functions, including visual acuity, visual field, and the peak time of flash visual evoked potential (F-VEP).[43] In addition, Young et al. suggested that the CFF test could better distinguish severe optic neuritis and non-arteritic anterior ischemic optic neuropathy (NAION) patients.[44] Recent research has revealed a significant decrease in patients with myopia greater than 8.0 D[45], which may be related to the thinning of the retinal ganglion cell layer due to axial growth. There are studies demonstrating the correlation between the CFF and electrophysiology tests. Patients who recovered from unilateral acute optic neuritis had lower CFF values but did not have significant change in P-VEP P100 latency compared to the unaffected eyes of patients and healthy volunteers. This suggested that the CFF device is a valuable tool for evaluating long-term optic nerve dysfunction.[46] Correlations between cerebral activity and the CFF value could be efficiently detected by an EEG, in which both CFF and alpha wave are attenuated as individuals age.[16] Furthermore, flicker positively affects memory accuracy in older people, with flicker frequencies at around 9.5–10.5 Hz[47], and the enhanced EEG amplitude responses could be observed between 5–15 Hz flicker frequencies simultaneously.[48]

4. Current research of CFF in cataracts

Patients with other eye diseases usually could not get an accurate assessment of the visual function recovery after cataracts surgery, particularly in patients with pre-existing fundus lesions, such as AMD, DR, and macular edema.[49,50] However, due to media opacity, patients often cannot undergo a thorough preoperative fundus examination. Even when the fundus is visible, further consideration is still required to assess whether surgery will have an additional benefit. Therefore, a visual function test independent of media opacity can be helpful for better evaluating postoperative visual function.

Studies have shown that the CFF measurement is not affected by media opacity in early-stage cataracts. An adequate flicker brightness can achieve a better accuracy for late-stage cataracts.[51,52] Furthermore, Douthwaite et al. showed that the CFF measurement is not affected in severe cataracts that were classified according to LOCS III grading criteria.[53] Besides, low variability and no statistical difference were found in CFF values between pre-operation and post-operation for severe cataracts, even when the logarithm of the minimum angle of resolution (logMAR) best-corrected visual acuity was 2.20 [54].

Usually, the media opacity leads to degradation of the quality of fundus imaging, which is thought to affect spatial resolution rather than temporal resolution,[55] and thus the CFF value should be relatively stable theoretically. Lachenmayr et al. simulated the media opacity caused by cataracts using several diopter spherical lenses and ointment with different densities. They confirmed that retinal image degradation caused by media opacity has a limited effect on the CFF value.[56] Moreover, Ikeda et al. reported that the magnocellular pathway could still respond to defocused image attenuation, which gives a plausible explanation for the independence of CFF tests from the image degradation caused by media opacity.[57]

Previous studies have found a decrease in the CFF value in patients with macular diseases, including AMD and DR.[40–42,58] This decrease may be attributed to the loss of retinal ganglion cells. Other studies have found alterations in CFF values in high myopia eyes,[45,59] indicating that CFF tests were sensitive enough to discern macular diseases and structural changes in the retina. Shankar et al. showed that the area under the

curve (AUC) was 0.93 with 88% sensitivity and 90% specificity in discriminating between healthy control and patients with fundus disease under a 1.5°flicker source, and larger flicker sources were less affected by the defocus caused by media opacity.[36,60] There were no significant differences in CFF values between patients with cataracts and patients with intraocular lenses (IOLs) under 1.5°visual angle and 38.2 cm observation distance. In contrast, a significant difference was found in macular disease patients with cataracts under the same conditions. There appears to be a significant correlation between the CFF value and logMAR visual acuity in macular disease eyes.[36]

5. Clinical studies of CFF as a potential vision test

A series of PVTs have been developed and used in various clinical studies. Besides CFF, potential acuity meter (PAM), laser interferometer (LI), super-illuminated pinhole (SPH), and optimal reading speed (ORS) have been used to predict post-cataracts visual acuity.

Romo et al. evaluated the postoperative visual acuity of 26 patients with cataracts and 26 cataract patients combined with ocular comorbidity. They found that the lower the CFF value recorded, the poorer the postoperative visual acuity might be. More importantly, there was a high correlation between the CFF value and visual acuity in patients with macular degeneration.[54] With cataracts progression, it is difficult to perform most PVTs, especially for PAM and LI measurements, both of which require visual acuity$\geq$ 20/40, whereas the CFF test is not affected under this condition.[61] PAM, LI, and ORS tend to underestimate the postoperative visual acuity to predict visual outcomes in patients with moderate and dense cataracts. On the other hand, CFF is better at predicting postoperative visual acuity, with 77% postoperative visual acuity within two lines in patients with moderate cataracts and 80% postoperative visual acuity within three lines in patients with dense cataracts.[54] In patients with moderate cataracts and healthy fundus, ophthalmologist judgment is superior to most PVTs for predicting postoperative visual acuity. However, in patients with dense cataracts or cataracts combined with fundus disease, the CFF test is more accurate than the ophthalmologist's judgement.[54] Therefore, these findings suggest that the CFF examination could provide more valuable information for patients with fundus disease.

Douthwaite et al. studied 88 cataracts patients divided into the following groups according to whether they present combined with fundus lesions, including 22 dry AMD, 11 glaucoma, 3 macular epiretinal membranes, 3 amblyopia, 2 wet AMD, and 1 macular hole. They found that both the CFF test and other PVTs tended to underestimate postoperative logMAR visual acuity in cataract patients combined with ocular disease. However, the CFF test had a minor mean bias with a prediction error ranging between three to five letters.[53]

In theory, the CFF value represents the limit of temporal resolution, and the best-corrected visual acuity represents the ability of spatial resolution. Thus, using the CFF test to assess postoperative visual acuity appears to be an indirect approach. However, retinal and optic nerve diseases usually adversely affect spatial and temporal visual functions. The CFF examination could help doctors to assess the possibility of fundus disease, especially in eyes with dense cataracts, and guide patients with a reasonable visual prognosis. Few studies have been reported in China on this topic, and the correlation between the CFF value and postoperative visual acuity and other visual functions needs further study.

6. Conclusions

As a small, portable tool, the CFF device does not require dilated pupils, and patients themselves can complete the measurement with simple training. It is easy to assess visual function by comparing it with the average age group. A standardized procedure can reduce measurement error and facilitate follow-up. The application of the CFF test in ophthalmology needs further research for early diagnosis and prognostic assessment.

Study approval

Not applicable.

Author contributions

ZL, ZY conceived and designed the study. GX wrote the initial draft. JF provided further editing. HQ executed the revision. LL, WC, YG, TM helped during the project. All authors read and approved the final version of the manuscript. All authors reviewed the results and approved the final version of the manuscript.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Abbreviations

CFF	critical flicker fusion frequency
AMD	age-related macular degeneration
PVT	potential visual test
SSRIs	selective serotonin reuptake inhibitors
DR	diabetic retinopathy
F-VEP	flash visual evoked potential
NAION	non-arteritic anterior ischemic optic neuropathy
EGG	electroencephalogram
logMAR	logarithm of the minimum angle of resolution
AUC	area under the curve
IOLs	intraocular lenses
PAM	potential acuity meter
LI	laser interferometer
SPH	super-illuminated pinhole
ORS	optimal reading speed
HPNS	high-pressure nervous syndrome

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.aopr.2022.10.002.

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