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Detection of Glaucoma Progression with Alternation Flicker

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Abstract Glaucoma is a progressive optic neuropathy characterized by functional visual loss and underlying optic nerve deterioration. Optic nerve imaging, achieved using photography and scanning ophthalmic laser diagnostic imaging techniques, is an important aspect of glaucoma diagnosis and management. Alternation flicker is a technique in which serial optic nerve photographs, typically taken one or more years apart, are aligned and alternated in order to allow the observer to easily detect change over time. Alternation flicker has been shown to improve several aspects of optic nerve evaluation and has been demonstrated to correlate with traditional glaucoma risk factors, with some limitations. In this review, we consider the literature with respect to flicker for the evaluation and monitoring of glaucomatous optic neuropathy.

Keywords Glaucoma · Structural progression · Imaging · Automated alternation flicker · Flicker chronoscopy · Optic nerve · Photography · Optic neuropathy

This article does not contain any studies with human or animal subjects performed by any of the authors.

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Introduction

Glaucoma is a progressive optic neuropathy that leads to irreversible visual loss. Functional impairment is accompanied by permanent damage to the retinal nerve fiber layer as well as structural changes such as disk hemorrhages (DHs), rim loss, and parapapillary atrophy. Diagnosis of progression requires evaluation of the optic nerve and assessment of these structural changes using optic nerve photos, but poor agreement among observers using side-by-side photographic interpretation has led to a lack of reliable clinical monitoring. Alternation flicker has long been explored for its utility in the assessment of glaucoma progression, and has shown promise in improving inter-observer reliability and increasing the sensitivity of detecting structural progression. Technological advances that allow for automated alignment and alternation of optic nerve photos make alternation flicker a powerful tool for use in routine clinical assessment.

Limitation of Side-by-Side Photographic Analysis and Optical Coherence Tomography

Evaluation of the optic nerve and retinal nerve fiber layer (RNFL) are fundamental to diagnosing glaucoma and detecting its progression, but limitations exist in photographic review and optical coherence tomography (OCT) algorithms. Importantly, there is consistent disagreement among experts viewing optic disk photographs. Intraobserver consistency in the measurement of cup:disk ratio along the horizontal and vertical axes when viewing stereo, color, and fundus photographs has been shown to be high

[kappa statistic (κ) = 0.82–0.86], with substantial agreement also existing for neuroretinal rim loss ($\kappa = 0.71$) [1]. However, agreement between observers is markedly lower ($\kappa = 0.58$–0.74), and patient stratification based on suspicion for glaucoma has no impact on reliability. The same poor interobserver agreement applies to the determination of structural progression using successive optic nerve photographs. When glaucoma specialists reviewed side-by-side optic disk photographs for signs of structural progression, there was poor interobserver reliability ($\kappa = 0.20$) and a 40 % false positive rate [2]. Because OCT can create automated, quantitative measurements of RNFL and optic nerve head parameters, it has been hoped that this approach would provide high sensitivity and specificity for glaucoma detection. However, one of the major limitations of OCT is the poor agreement between RNFL degeneration and visual field loss ($\kappa = 0.09$) in progression detection [3]. It has been shown that regions of RNFL degeneration can go undetected due to a normal average RNFL thickness according to OCT. Specifically, the inferotemporal retinal region, which has an established high sensitivity and specificity for discriminating glaucomatous from non-glaucomatous eyes, is also the area that most frequently shows progression with regional RNFL thinning despite normal average RNFL thickness [3]. Importantly, the vast majority of eyes (45 of 56 in this particular study) showed localized thinning before more diffuse loss occurred.

The causes for undetected regional thinning are threefold: (1) the persistent thickness of certain retinal segments; (2) the incorporation of non-retinal structures into RNFL thickness measurements; and (3) the use of a cluster-based threshold definition for abnormality in OCT algorithms. Average papillary RNFL height is highest in the superior and inferior portions of the disk, creating a "double hump" pattern on OCT that can be preserved even in the setting of diffuse nerve fiber degeneration [4]. The temporal sector, corresponding to the papillomacular bundle, is also relatively thick throughout the disease course and accounts for preserved central vision until late-stage disease [3]. This isolated thickness leads to elevated average RNFL thickness measurements that mask localized thinning. In addition, the average RNFL thickness can be artificially elevated by the integration of edema, epiretinal membranes, and blood vessels into the OCT algorithm, despite regional thinning [5]. Finally, there is a greater rate of RNFL thickness change in glaucoma among those with high baseline thickness simply because they have more apparent RNFL to lose. As a result, individuals with a relatively thick RNFL when healthy will be more likely to reveal abnormalities of standard automated perimetry before a statistically significant RNFL abnormality is noted by OCT [6]. In instances where OCT fails to meet the cluster definition of abnormality, localized thinning can often be noted in the same regions where multifocal visual evoked potential and perimetry reveal abnormalities [7].

In sum, limitations in side-by-side photographic review techniques and OCT algorithms undermine the reliable, accurate detection of glaucoma progression.

History of Manual and Automated Flicker

Since its first description by Bengtsson and Krakau [8, 9] in 1979, the rapid alternation of successive optic nerve images has been recognized as a sensitive technique for detecting structural progression in glaucoma. Alternation flicker relies on the precise alignment of baseline and follow-up photographs to convey meaningful changes. Initial techniques to achieve the alignment and alternation of sequential optic nerve photographs included the use of two overlapping slide projectors and custom computer imaging programs in which corresponding image features required 6 points of manual (mouse-click) registration prior to the generation of aligned images. Although it has continued to be intermittently explored in glaucoma research over the past several decades, this technique remained under-utilized due to technological limitations that made its adoption into daily practice burdensome.

Stereoscopic image review is one of the earliest forms of image analysis, and it allows structural changes to be perceived as depth. However, this method is vulnerable to photographic artifacts and variations between left and right stereo pairs [10]. As a result, strategies for aligning the two photos to minimize non-meaningful change have been developed. Manual registration (i.e. spatial alignment) and scaling of successive optic nerve photographs can achieve a high precision of between 1 and 3 pixels, providing a sensitive method for monitoring structural progression when images are presented in rapid sequence (e.g. using a television monitor or overlapping slide projectors) [10, 11].

Ultimately, variability of photographic techniques, relatively poor fundus photograph quality, and lack of digitized images or automated registration has historically limited the sensitivity and reproducibility of this promising technique.

With greater computerization in the clinical practice of ophthalmology, fundus photographs have increasingly become automatically digitized. This allows for new opportunities in image registration algorithms, as automated registration is more accurate, repeatable, and freer from investigator bias or error than methods that depend on manual registration. Image registration is now utilized in most fields of medicine (particularly radiology), and Maintz and Viergever [12] have provided a comprehensive survey of the current literature. Alignment of optic nerve photos requires intrinsic registration, relying on photographic

landmarks, segments, object surfaces, or voxel properties to align the images. Multiple registration algorithms exist, and an understanding of the source of baseline variation between two images attempting to be aligned is critical to selecting the appropriate registration technique to retain meaningful changes while eliminating artifact [13].

The automated alternation flicker (AAF) algorithm automatically registers and matches serial photographs to the subpixel level. This algorithm identifies features—such as intersections of retinal or choroidal vessels—in each photograph and aligns images using such digitally identifiable features. The algorithm applies global transforms until the best match is achieved between two images. Color and illumination are not altered [22]. Alternation flicker of two digitized images registered with a non-rigid polynomial-warping algorithm was shown to be 90 % concordant with standard stereoscopic inspection with no false negative results [14].

Why is Photography So Important?

Recent studies demonstrate that optic nerve photography is being performed less frequently than optic nerve imaging. Swamy et al. described how optic disk imaging in glaucoma cases or in glaucoma suspects may not meet American Academy of Ophthalmology guidelines. Although both techniques are underused, optic disk photos are particularly under-employed compared to scanning computerized ophthalmic diagnostic imaging (SCODI). In this retrospective, Medicare claims-based study, the authors reveal that 20 % of patients received SCODI and only 6 % were photographed in the first quarter of diagnosis of glaucoma or glaucoma suspect [15•]. Stein et al. [16] report how with both optometrists and ophthalmologists, the probability of undergoing fundus photography among individuals with open-angle glaucoma or suspected glaucoma enrolled in a managed care network was relatively low (13–25 %). Possible explanations for the trend away from photography toward SCODI include increased time and pupillary dilation requirements of photography compared to SCODI, the reliance on normative databases in SCODI for diagnosis, and perceptions that SCODI reimburses more than photography. This trend is disappointing; as discussed below, photography, especially when combined with flicker, has several advantages over traditional forms of detecting structural progression.

Advantage of Flicker for Detecting Various Forms of Structural Progression

Many reports have described the advantages of flicker for detecting structural glaucomatous progression. Flicker enhances the detection rates of progressive glaucomatous optic neuropathy compared to traditional forms of photographic assessment. VanderBeek et al. used two graders who assessed a set of optic nerve head photographs for progressive parapapillary atrophy (PPA), and then evaluated photographs using AAF. Both graders identified significantly more cases of PPA progression using AAF compared to photography (27–34 vs. 8–13 %; both $p = 0.003$), suggesting that AAF improves the detection of progressive PPA [17•]. Similarly, Syed et al. obtained serial sets of optic nerve photographs from 394 eyes, and seven graders reviewed images and assessed the presence of DHs. The authors founds that the sensitivity of AAF for DH detection was higher than side-by-side photographic analysis (0.878 vs. 0.705; $p = 0.002$) and single photographs (0.878 vs. 0.757; $p = 0.01$), indicating that AAF is more sensitive than current clinical standards for DH detection [18••]. Apart from the detection of PPA and optic DHs, flicker has been shown to have a heightened sensitivity for detecting early glaucoma. Funk et al. [19] quantified the sensitivity of alternation flicker for the detection of glaucomatous optic nerve changes, and found it to be 90 %. Heijl and Bengtsson [11], in their early description of alternation flicker, demonstrated its higher sensitivity relative to conventional non-flickered comparisons of the optic disk, suggesting that flicker may provide a significant improvement over standard methods of analyzing serial optic nerve photography. Furthermore, alternation flicker facilitates detection of glaucomatous optic disk changes as indicated by changes in vessel position, color, and other cues for contour change, and in many cases, re-inspection of stereophotographic comparison led to a revised judgment on the basis of disk changes rendered more obvious with alternation flicker [14]. Despite its importance in glaucoma monitoring, optic disk evaluation shows poor agreement among evaluators [2]. Flicker has been shown to improve inter-grader agreement compared to other forms of optic nerve assessment. For example, Radcliffe et al. [20•] demonstrated that compared to evaluation of sequential images using stereophotography; overall inter-grader agreement among four graders was better with AAF for assessing blood vessel movement. Of note, overall agreement in this study was worse for DH using AAF compared to stereophotography. Cymbor et al. [21] demonstrated that compared to traditional side-by-side photographic assessment of sequential optic nerve head photos, flicker demonstrated better concordance among examiners in judging glaucomatous progression. Finally, VanderBeek et al. demonstrated that interobserver agreement between observers using AAF was significantly higher than using photographs when evaluating for PPA progression [22]. Syed et al. [22] demonstrated a method to assess optic nerve head changes using a combination of both AAF and

stereophotographic optic nerve images, a technique that may optimize the detection of early structural glaucomatous changes and enhance clinical identification of progressive glaucomatous optic neuropathy. Further research will need to be performed to determine whether this combination of AAF and stereophotography has an advantage over AAF alone in the detection of various forms of glaucomatous optic neuropathy. Finally, we recently evaluated the ability of AAF to assist with the identification of preperimetric glaucomatous progression (unpublished data by Syed et al.). In this study (which received Institutional Review Board approval from Weill Cornell Medical College), a database of 407 individuals under surveillance for glaucoma development or progression was reviewed. Baseline and follow-up optic nerve head photographs were obtained and used to create AAF images. Two masked graders determined which eyes had evidence of glaucomatous structural progression. Twenty-two eyes met inclusion criteria, with a normal result on standard automated perimetry and a normal or borderline RNFL thickness on tomography after the period of structural progression. All available visual field and tomography results were reviewed for each eye. While all study eyes had normal visual fields at the time of follow-up photography, 7 (32 %) developed subsequent abnormal fields. Five eyes (23 %) with normal or borderline tomography at the time of follow-up photography developed subsequent abnormalities. The conclusion from this study was that AAF might allow for early detection of structural injury in glaucoma, showing changes even before perimetry or optic nerve OCT become abnormal.

Using Automated Flicker to Identify Other Glaucoma Risk Factors

In addition to the advantages provided by alternation flicker over traditional forms of optic disk analysis in the evaluation of glaucoma, flicker has been shown in several studies to be useful in the identification of several risk factors for glaucoma progression. For example, McGlynn et al. used flicker chronoscopy to evaluate the relationship between vascular risk factors and structural glaucomatous progression. After analyzing 72 eyes, the authors found that 40 patients with some form of structural progression had lower diastolic blood pressure than the 32 patients without any progression (71.8 vs. 76.5 mmHg; $p = 0.02$). A similar proportion of patients with RNFL progression and neuroretinal rim loss had lower diastolic blood pressure compared to those without these structural changes. This study therefore used flicker to reveal a correlation that may have significant implications for glaucoma management [23]. Similarly, Chee et al. performed a study in which two glaucoma specialists assessed serial flicker chronoscopy images for features of structural progression, and found that age was significantly associated with global (OR = 1.8 per year, $p < 0.001$) and PPA progression (OR = 1.7 per year, $p = 0.002$), and lower corneal hysteresis was associated with global progression (OR = 0.78 per mmHg, $p = 0.049$) and RNFL loss (OR = 0.5 per mmHg, $p = 0.02$) [24•]. Finally, one study involved graders reviewing serial photographs aligned with AAF, and images were evaluated for the presence of retinal blood vessel positional shifts. After two graders reviewed 158 image sets from glaucomatous eyes, it was determined that eyes with blood vessel shifts progressed more rapidly than those without (−0.55 vs. −0.29 dB/year, $p = 0.03$), and the presence of either mild or moderate visual field progression (compared to no progression) was associated with the occurrence of blood vessel shift (OR = 2.2, $p = 0.03$). Furthermore, neuroretinal rim loss and DH were significantly associated with blood vessel shift [25].

Correlation with Perimetry

The reported correlation between glaucomatous optic disk progression and visual field changes has been inconsistent. Several investigations have reported a relationship between structural and functional deficits in glaucoma, with structural transformations usually preceding functional loss [26]. Furthermore, in cases of focal optic nerve damage, there appears to be a topographic correlation between structural and functional losses [26]. A similar relationship has been shown using flicker; Heijl and Bengtsson found flicker analysis of serial optic disk photographs to provide results that correlated with computerized threshold perimetry. In their study, of the 12 eyes that developed visual field defects over time, ten showed highly suspected or definite changes in the optic disk [11]. On the other hand, the Early Manifest Glaucoma Trial compared glaucomatous eyes that were undergoing treatment to a control group, and found minimal agreement between optic disk progression using flicker and visual field progression [27]. Of the 136 eyes that demonstrated progression, 117 exhibited progression in visual field outcome only while one demonstrated progression in optic disk outcome only. Only 18 progressed based on both visual field and optic disk outcomes. Importantly, the study protocol for reviewing images was designed for high specificity; it required concordance among three graders after analyzing two sets of photographs using flicker and side-by side viewing [27]. Radcliffe et al. studied serial photographs of glaucomatous eyes with at least 36 months of follow-up that were reviewed by four graders. In this study, the agreement between perimetric (defined using point-wise

linear regression criteria) and disk progression (including rim change, DH, and vessel movement) using flicker was poor ($\kappa = 0.19$) [20•].

Challenges with Flicker

Like all optic nerve imaging techniques, alternation flicker has several notable limitations. To begin, flicker will only be as good as the baseline images from which it is comprised, and as such flicker will be limited by images with media opacity (or differences in media opacity between the two images), by misalignment (which can cause parallax, diskussed further below), or by significant differences in illumination or hue, as can occur with serial images in which the baseline and follow-up images were taken by different cameras. Similar artifacts can occur using any type of SCODI imaging, but these artifacts will be more apparent using alternation flicker as the analysis of images is subjective. Subjective analysis of images is an additional limitation of flicker, and above we have presented a range of levels of agreement between graders from low to reasonably high, though in general the technique performs better than side-by-side photographic evaluation for a variety of tasks [24•, 28]. False-positive results are possible with AAF, and a criticism of AAF is that the matching algorithm can generate artifacts and cause an artificially elevated level of sensitivity and reduced specificity. This has also been described with non-automated alternation flicker techniques. Indeed, parallax is as frequent with serial side-by-side photographs, but is unnoticed by graders because the technique overall is less sensitive. With experience, the grader may be able to distinguish false positives generated by flicker from true progression. Instructing a photographer to center all images in a similar manner, or to match follow-up and baseline images if the baseline image is off-center, will reduce parallax. Since the AAF algorithm applies a global transformation to images, small regions of focal change (such as the appearance of a linear RNFL defect or a focal neuroretinal rim notch) without surrounding change are likely to represent true change. Global optic nerve changes, such as an overall thinning of the rim and retina, particularly if only in one axis, are more likely to represent parallax [8]. To improve the detection of structural progression with flicker chronoscopy, we have produced color subtraction maps that highlight differences between baseline and follow-up photographs (Figure 1). This technique has shown strong sensitivity for detecting parallax as well as features of structural progression in glaucoma [29].

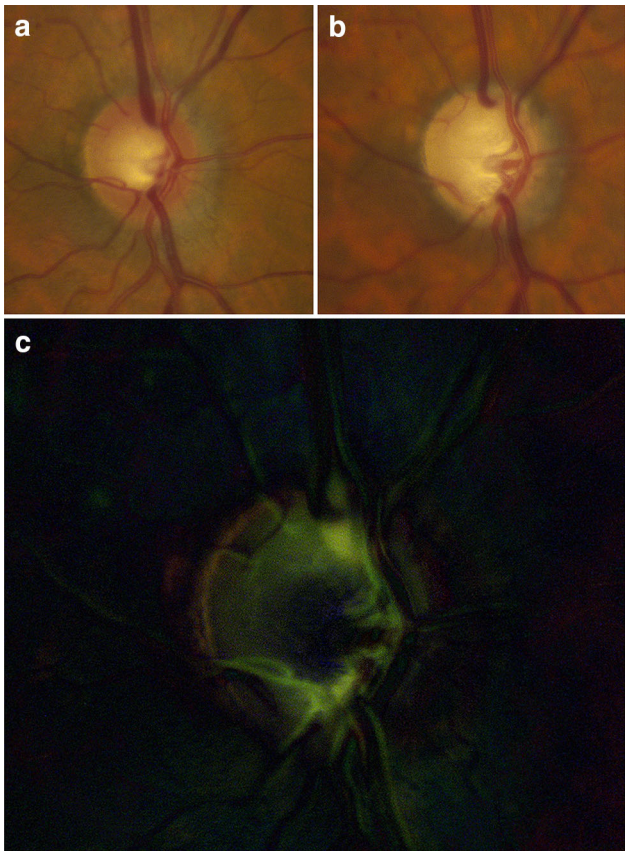

Fig. 1 Because changes observed with flicker chronoscopy may be difficult to view in print, we have produced a color subtraction map demonstrating the difference between the baseline (**a**) and follow-up (**b**) digitally aligned photographs. In **c**, the subtraction map demonstrates significant progression (in *green*) for areas of neuroretinal rim loss (Color figure online)

Conclusion

In conclusion, flicker has great potential in the management of glaucoma. The technique has demonstrated significant advantages for the evaluation of PPA progression and DH. Flicker has also been used to confirm other risk factors for glaucoma progression (such as age and low corneal hysteresis). Flicker has recently been used to identify new features of glaucoma progression, such as retinal blood vessel movement, indicating that this technique may lead to significant advances in our understanding of glaucoma. Given that flicker is only weakly associated with visual field loss and has not been compared to progression with OCT, there are still many opportunities for further research. Limitations of image quality, subjective evaluation, and parallax pose the most significant problems for the technique.

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- • Of importance
- •• Of major importance

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