UCSD ISP Draft by Jagannath Sam Nayak

Title: Confocal Scanning Laser Ophthalmoscopy (CSLO)-based Topographic Change Analysis in Progressing Glaucomatous and Stable Eyes.

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Abstract:

Purpose: To assess the performance, in an independent population, of previously published confocal scanning laser ophthalmoscopy Topographic Change Analysis (TCA) parameter cut-offs for discriminating between progressing glaucoma, stable glaucoma, and healthy eyes.

Methods: Five published TCA cut-offs[10,14] were applied to the following 4 groups: 54 glaucomatous eyes (at study baseline examination) progressing by optic disc stereophotograph assessment, 79 glaucomatous eyes progressing by standard automated perimetry guided progression analysis (GPA), 72 stable glaucoma eyes (patients tested 5 times over 5 weeks), and 135 healthy eyes. All eyes were imaged at least four times by Heidelberg Retina Tomograph (HRT; Heidelberg Engineering, Heidelberg, Germany) as part of the Diagnostic Innovations in Glaucoma Study (DIGS) and African Descent and Glaucoma Evaluation Study (ADAGES). Sensitivity and specificity for classifying progressed and stable eyes, respectively. were reported.

Results: The two TCA parameters providing the best sensitivity/specificity trade-off were the 95% cut-off for the largest clustered super-pixel area within the optic disc margin[10] (sensitivity of 0.922 in stereophotograph progressors and specificity of 0.778 in stable glaucoma eyes) and the Moderate Criteria (largest clustered superpixel area within the optic disc margin ≥1% of the disc area with ≥50 μm mean depth change)[14] (sensitivity of 0.906 in stereophotograph progressors and specificity of 0.708 in stable glaucoma eyes). These cut-offs detected progression over a similar time frame. Specificity in healthy eyes was lower than in stable glaucoma eyes.

Conclusions: Previously published HRT TCA parameters can discriminate between progressing and stable glaucoma eyes in an independent population with good sensitivities and specificities. Low specificity of TCA in healthy eyes might be due to the effects of aging on optic disc topography, evidenced by the long follow-up in this group.

Introduction:

The most common type of glaucoma, primary open-angle glaucoma (OAG), has no noticeable signs or symptoms except gradual peripheral vision loss which may not be noticed until the disease is at an advanced stage[1]. The difficulty of early diagnosis of glaucoma has made it the second leading cause of

blindness in the world, affecting more than 66 million people internationally, and leaving at least 6-8 million blind in both eyes[2,3].

Although subjective clinical examination and fundus photograph assessment are the most common ways of detecting structural change in glaucoma and monitoring its progression, advances in computerized imaging technology such as CSLO, scanning laser polarimetry, and the more recently developed spectral domain optical coherence tomography allow objective evaluation of the optic disc and retinal nerve fiber layer (RNFL)[4,5,15]. These technologies provide quantitative measurements that are highly reproducible, can assist the clinician in glaucoma diagnosis/monitoring, and offer considerable opportunity for use as efficacy endpoints in clinical trials.

CSLO is an ophthalmic imaging technology that uses laser light instead of a bright flash of white light to illuminate the retina. Confocal imaging is the process of scanning an object point by point by a focused laser beam and then capturing the reflected light through a small aperture (a confocal pinhole). The confocal pinhole suppresses light reflected or scattered from outside of the focal plane, which otherwise would blur the image. (Figure 1). The result is a sharp, high contrast image of the object layer located at the focal plane. (Figure 2)

The advantages of using CSLO over traditional fundus photography include improved image quality, small depth of focus, suppression of scattered light, patient comfort (through less bright light), 3D imaging capability, video capability, and effective imaging of patients who do not dilate well. Because diabetics typically do not dilate well and account for a large number of patients with vision problems, CSLO imaging is a valuable tool for most eye care providers.

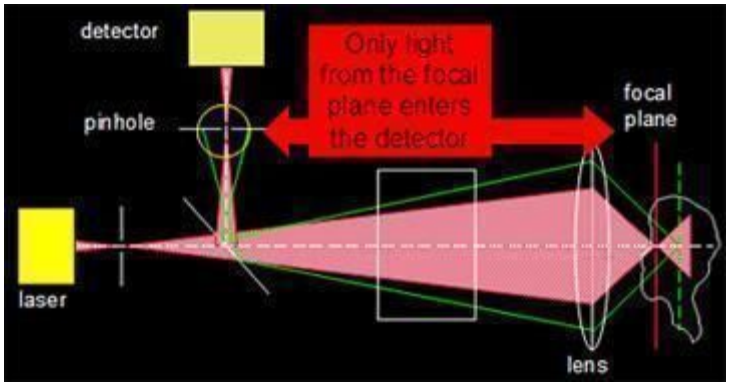

Figure 1. Confocal scanning laser ophthalmoscopy (CSLO). CSLO images the retina by scanning the optic disc with a laser beam. The reflected light is measured through a pinhole in order to minimize scatter, and produce a clear image of the focal plane.

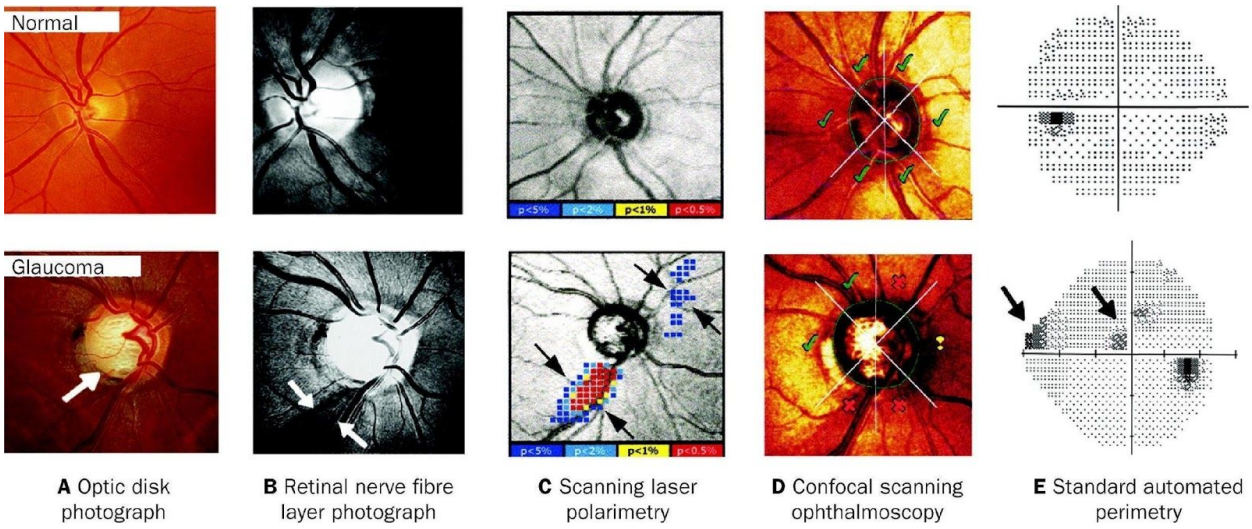

Figure 2. Assessment of the optic disc in healthy and glaucomatous eyes: (A) Optic nerve photography: small central cup in healthy eye; enlarged cup and loss of inferotemporal neuroretinal rim (arrow) in glaucomatous eye. (B) Retinal nerve fiber layer photography: uniform reflections in healthy eye; poor reflections in inferotemporal region (arrows) in glaucomatous eye. (C) Scanning laser polarimetry: no identified retinal nerve fiber layer defects in healthy eye; retinal nerve fiber layer thickness is reduced inferotemporally and superonasally (arrows) in glaucomatous eye. (D) Confocal scanning laser ophthalmoscopy: neuroretinal rim area is within normal limits (ticks) in healthy eye but reduced in inferior and superonasal regions (crosses) in glaucomatous eye. (E) Standard automated perimetry: central scotoma and superior scotomas corresponding with inferior structural defects (arrows) in glaucoma. Images taken from Weinreb and Khaw[1].

CSLO is a proven technique for identifying eyes with glaucomatous optic disc damage.[6] The primary method for assessing glaucomatous change using CSLO is TCA with the HRT.[7] TCA is a technique that uses a nested three-way ANOVA model to compare the variability within a baseline examination to that between baseline and follow-up examinations, while controlling for topographic scan variability, scan time (i.e., baseline or follow-up), and location of topographic height measurements. TCA visually presents clusters of superpixels which are counted to describe the size and location of regions of change compared to baseline images. TCA flags progression when change exceeds measurement variability and is confirmed on multiple tests; instrument defined progression is defined as a cluster of 20 or more significantly depressed superpixels within the optic nerve head margin.[8]

Although various types of optic disc changes can be quantified using CSLO, it remains unclear what exactly defines a clinically significant change upon follow-up examination. In order to detect disease-related change it is crucial to be able to differentiate between small physiologic changes present in healthy eyes and small-pathologic OAG related changes. Despite recent advances in the field, there are still no accepted standards for detecting or predicting OAG structural change using CSLO. It is hypothesized that a small physiologic regional susceptibility of the neuroretinal rim area (NRA) may be accelerated in glaucoma, resulting in differences in the rate and pattern of changes identified in healthy eyes compared to glaucomatous eyes[9]. The improved reproducibility of CSLO and other imaging instruments makes them valuable tools for evaluating the optic disk.

There have been very few studies evaluating the ability of TCA parameters to discriminate between longitudinally observed progressing [by stereography or Standard Automated Perimetry (SAP) Guided Progression Analysis (GPA)] and stable eyes[10]. Because of this, there is a need for a set of predefined common criteria for TCA parameters to improve agreement between physicians in assessing TCA defined progression.[11] Additionally, optic nerve head depression, as measured by TCA, has already been shown to occur before RNFL thinning, as measured by stereophotograph assessment (current gold standard), in a significant proportion of patients with glaucoma. A new and accurate set of TCA parameters could create a time window for therapeutic intervention to slow or prevent observable RNFL thinning in glaucoma.[12]

The study aims to describe the performance, in an independent population, of previously published TCA parameter cut-offs[10,14] for discriminating between progressing glaucoma, stable glaucoma and healthy eyes. Assessing the performance of suggested TCA cut-offs for defining progression in an independent sample may help determine which cut-offs are most likely to be acceptable, generalizable standards.

Materials and Methods:

Patients:

CSLO data sets were obtained from the Diagnostic Innovations in Glaucoma Study (DIGS) and African Descent and Glaucoma Evaluation Study (ADAGES). DIGS is a prospective, longitudinal observational cohort study being conducted at the University of California, San Diego Hamilton Glaucoma Center which is evaluating the relationship between changes in the structure of the eye and the vision loss caused by glaucoma. ADAGES is an ongoing multicenter study prospectively designed to assess structure and function in glaucoma. The study is being conducted at the University of California, San Diego Hamilton Glaucoma Center, the University of Alabama at Birmingham (UAB), and the New York Eye and Ear Infirmary (NYEE)[13]. Consistency of testing procedures across various sites is ensured through a number of protocols set in place. The study currently includes over 200 healthy participants with a mean follow-up with the Heidelberg Retina Tomograph (HRT) of 4.6 years (and a mean of 3.8 visits), as well as 250 glaucoma patients with a mean follow-up of 5.7 years (with annual visits).

Inclusion/Exclusion Criteria

Inclusion

In order to be included in this study, participants needed to have open iris-cornea angles, best-corrected visual acuity of 20/40 or better, spherical refraction within 5.0 diopters (D), and cylinder correction within 3.0 D. In addition, participation required stereoscopic photographs of adequate quality and reliable (defined as 33% or fewer false-negative errors, false-positive errors, and fixation losses) visual field results on all tests.

Exclusion

Participants with a history of intraocular surgery (except for glaucoma or uncomplicated cataract surgery), with diseases affecting the visual field, using medications known to affect visual field sensitivity, or with problems affecting color vision other than glaucoma all were excluded from this study. Participants with a family history of glaucoma were not excluded.

All participants underwent slitlamp biomicroscopy, Intraocular Pressure (IOP) measurements, and dilated stereoscopic fundus examination in order to rule out the presence of other ocular diseases. Stereoscopic photographs were taken within 6 months of the visual field tests and evaluated using a stereoscopic

viewer (Asahi Pentax Stereo Viewer II; Asahi Optical Co, Tokyo, Japan). Glaucomatous optic neuropathy was defined by evidence of neuroretinal rim narrowing or notching or focal or diffuse nerve fiber layer thinning.

Visual Field Test:

Visual function was assessed using SAP. SAP is a nonselective test, in that all types of retinal ganglion cells are able to detect the target, which measures Differential Light Sensitivity (DLS). DLS is the ratio of the background luminance (LB) to the varying stimulus luminance, known as the threshold differential luminance (DLT). Each participant underwent SAP using the Humphrey Field Analyzer II's 24-2 program, with the Swedish Interactive Thresholding Algorithm (SITA) (Carl Zeiss Meditec, Inc, Dublin, California). The target used in this chromatic test is a small (0.43°) flash of white light presented on a dim background (31.5 apostilbs) for 200 milliseconds.

Classification of eyes:

Each patient's eyes were classified as progressing glaucoma, stable glaucoma, or healthy. Progressive glaucoma was defined as narrowing of the neuroretinal rim, increase in RNFL defect size or the appearance of a new RNFL defect on stereophotograph assessment. Stereophotograph assessment was based on masked (patient name and diagnosis) comparison between the baseline and most recent photograph, by two observers. If these observers disagreed, a third observer adjudicated the results. Alternatively, eyes were assessed as progressing if the SAP GPA analysis indicated "likely progression" (based on three or more consecutive visits with ≥ 3 progressing points compared to baseline variability measurements). Glaucomatous eyes were classified as stable if they were imaged over 5 visits in 5 consecutive weeks (glaucoma does not progress in weeks). Eyes were deemed to be healthy only if both eyes had normal ophthalmological examination, healthy optic disc based on stereophotograph assessment, IOP $\leq$ 21mmHg, and absence of repeatable visual field damage.

TCA processing:

All examinations in the study were conducted with the same model of HRT and with the same version of analysis software. Using the HRT 3 system software (ver. 3.1.2; Heidelberg Engineering), the follow up examinations underwent topography alignment with the baseline topograph of each eye for TCA quantitative analysis which provided superpixel change probabilities.

The change probability values and the superpixel mean difference image produced by the HRT software were used to create a change significance map for each follow-up examination. The map indicated locations with significant decrease in retinal height, based on a negative height change in the mean difference image with change probability < 0.05. All data analysis was performed with MatLab, ver. R2007a.

Any significantly changed superpixel location with fewer than four significantly changed superpixel neighbors was considered clinically insignificant and was filtered.[10] Clinically significant TCA change locations were defined as superpixel locations with changes repeatable in two of the two, three of the three, or three of the four most recent follow-up examinations, depending on the number of follow-up examinations available.

The TCA parameters, which describe the change significance maps, being investigated are those previously suggested[14] and used[10]. These parameters describe aspects like the cluster of superpixels with the largest significant change in area or the cluster size in superpixels expressed as a percentage of optic disc area, or many other facets of the map.

TCA parameters:

The previously published TCA parameters tested in our independent population were:

1) Liberal criterion which required the largest clustered superpixel area within the optic disc margin≥0.5% of the disc area and a depth change of ≥20 μm[14]
2) Moderate criterion which required largest clustered superpixel area within the optic disc margin ≥1% of the disc area, and a depth change of ≥50 μm[14]
3) Conservative criterion which required largest clustered superpixel area within the optic disc margin ≥2% of the disc area and a depth change of ≥100 μm[14]
4) 95% cut-off for the largest clustered super-pixel area within the optic disc margin[10]
5) 90% cut-off for the largest clustered super-pixel area within the optic disc margin[10]

Population and testing parameters:

A group of 133 eyes that were categorized as glaucomatous progressors by stereophotograph assessment or GPA (current gold standards) were considered true positives for analyses. The previously developed

parameter cutoffs were applied in these eyes in order to calculate their sensitivity. Additionally, TCA cut-offs were applied to the 72 stable glaucoma eyes. By definition, these eyes have not progressed over the 5 weeks timespan. TCA cut-offs also were applied to 134 healthy eyes. This allowed for assessment of the efficacy of cSLO TCA parameters for characterizing the differences between glaucomatous changes and physiologic changes in healthy eyes. Both stable glaucoma and healthy eyes were considered true negatives to calculate specificities.

Results:

Eyes meeting the inclusion and exclusion criteria described, as well as fitting the various classifications (stereophotograph progressors, GPA progressors, stable eyes, and healthy eyes) made up the study population. The study population is described below in Table 1. Means and associated standard deviations suggest that glaucoma patients had similar ages and visual field mean deviations (representing disease severity) at baseline.

	Stereophotograph Progressors	GPA Progressors	Stable Eyes	Healthy Eyes
No. of Patients	54	69	43	67
No. of Eyes	54	79	72	134
Age (SD), years	59.4 (12.7)	66.5 (9.9)	70.8 (10.0)	50.4 (13.5)
Follow-up time (SD), years	7.93 (1.29)	5.20 (2.55)	0.09 (0.03)	5.04 (2.0)
Number of scans (SD)	9.74 (2.61)	4.85 (1.63)	4.47(0.68)	5.98 (2.54)
Mean Deviation (SD), dB	-4.48 (5.49)	-3.21 (4.53)	-4.00 (5.30)	-1.88 (2.61)

Table 1. Study population statistics. The number of patients, number of eyes, average and standard deviation of age in years, average and standard deviation of follow up time in years, average and standard deviation of total number of scans, and the mean deviation (a measure of visual field) and its standard deviation for each study population group: stereophotograph progressors, GPA progressors, stable eyes, and healthy eyes.

The two TCA parameters providing the best sensitivity/specificity trade-off were: the 95% cut-off for the largest clustered super-pixel area within the optic disc margin[10] (with a sensitivity of 0.922 in stereophotograph progressors and a specificity of 0.778 in stable glaucoma eyes) and the Moderate Criteria (with a sensitivity of 0.906 in stereophotograph progressors and a specificity of 0.708 in stable glaucoma eyes), which used cut-offs of the largest clustered superpixel area within the optic disc margin

≥1% of the disc area with ≥50 µm mean depth change[14] (see Table 2). These cut-offs detected progression over a similar time frame. Specificity in healthy eyes was lower than in stable glaucoma eyes for all cut-offs investigated. Sensitivities and specificities for all cut-offs for all groups are shown below.

TCA Cutoff	Sensitivity stereophotograph progressors	Time to progression (SD) stereophotograph progressors	Sensitivity in GPA progressors	Time to progression (SD) in GPA progressors	Specificity in stable eyes	Specificity in healthy eyes
Liberal	0.953	4.37 (1.31)	0.869	3.34 (1.51)	0.458	0.178
Moderate	0.906	4.91 (1.62)	0.586	3.86 (1.97)	0.708	0.570
Conservative	0.547	5.04 (1.64)	0.182	4.45 (2.16)	0.986	0.963
Disk Area 90%	0.938	4.66 (1.42)	0.697	3.77 (2.01)	0.694	0.304
Disk Area 95%	0.922	4.82 (1.55)	0.545	3.88 (1.96)	0.778	0.593

Table 2. Sensitivity and Specificity performance of variance cutoffs.

Discussion:

The "best" performing TCA cut-offs (Moderate Criteria and 95% Disk area cut-off) could be considered as possible objective TCA standards for defining HRT-based progression, based on their ability to discriminate between progressing glaucomatous eyes and stable glaucoma eyes, as indicated by the sensitivity and specificity calculated. The specificity of these cutoffs was less than 1.0 in stable eyes. This indicates that TCA is attributing measurement variability to real change. The specificity of these cutoffs also was less than 1.0 in healthy eyes. This indicates that TCA is detecting real change caused by aging (i.e., physiologic change). Future studies should attempt to disassociate longitudinal change caused by progressing glaucoma from that caused by natural aging and should identify TCA cut-offs that are less sensitive to detecting measurement variability in stable eyes.

Greater TCA-defined progression in eyes progressed by stereophotograph assessment than in eyes defined as progressed by GPA is expected because both TCA and assessment of stereophotographs are indicators of structural change. This fact might introduce a bias in reported TCA sensitivities and may be a potential limitation of the current study, although the sensitivity of all cut-offs was assessed for both stereophotography and GPA.

Conclusions:

Based upon the performance of the five published TCA cut-offs, in our independent data set, two primary definitions for clinically significant change upon follow-up examination via CSLO were recognized: 95% cut-off for the largest clustered super-pixel area within the optic disc margin and the Moderate Criteria (largest clustered superpixel area within the optic disc margin ≥1% of the disc area with ≥50 μm mean depth change). Based on their sensitivity/specificity trade-offs these TCA parameters demonstrated an ability to discriminate between longitudinally observed progressing (by SAP and GPA) and stable eyes. Hopefully in the future, this information will be helpful in establishing a set of predefined common criteria for TCA parameters in assessing TCA defined progression. In spite of the strong ability to distinguish between progressing and stable glaucomatous eyes with TCA parameter cutoffs, there is need for further investigation to better elucidate the ability for these cut offs to 1) create a time window for therapeutic intervention before there is observable RNFL thinning in glaucoma and to 2) distinguish between changes associated with progressing glaucoma and those associated with the physiologic changes of aging.

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