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Journal

Journal of Glaucoma, 30(3)

ISSN

1057-0829

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Publication Date

2021-03-01

DOI

10.1097/ijg.0000000000001727

Peer reviewed

Nocturnal Variability of Intraocular Pressure Monitored with Contact Lens Sensor is associated with Visual Field Loss in Glaucoma

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Key words: glaucoma, intraocular pressure, glaucoma progression, visual field progression

ABSTRACT

Purpose**:** To determine whether 24-hour recording of intraocular pressure (IOP)-related ocular dimensional changes with a contact lens sensor (CLS, Triggerfish, Sensimed) is associated with the rate of visual field progression in primary open-angle glaucoma (POAG) patients.

Design: Retrospective, observational cohort study.

Participants: Patients with POAG were included from the Glaucoma Clinic and Diagnostic Innovations in Glaucoma Study at the Hamilton Glaucoma Center at University of California San Diego.

Methods: A session of 24-hour CLS recording was acquired for one eye from each patient. The mean follow-up time was 9.9 ± 4.0 years. The association between CLS variables and rate of change of mean deviation (MD) was determined by univariate and multivariate mixed linear regression models.

Results: Thirty-two patients, aged 69.8 ± 13.6 years were included, 50% were female. An average of 11.6 ± 5.6 SAP examinations was available with a mean rate of MD progression of -0.2 ± 0.4 dB/year. Mean IOP was 17.8 ± 4.2 mmHg. The mean number of IOP-lowering medications were 1.2 ± 1.0. Each 10-unit larger nocturnal variability of IOP-related ocular dimensional changes measured by CLS recording was significantly associated with -0.25 ± 0.11dB faster visual field loss in POAG patients (P = 0.035).

Conclusions: 24-hour CLS recording of IOP-related ocular dimensional change was associated with faster visual field progression. Such CLS recordings are useful to assess the risk of in progression in POAG patients.

INTRODUCTION

Elevation of intraocular pressure (IOP) is the major and only modifiable risk factor for the onset and progression of vision loss in glaucoma patients[1]. Clinical assessment of IOP is usually performed as a single measurement with Goldmann Applanation Tonometry (GAT) during office-hour visits. A major limitation of GAT-based IOP assessment is that IOP-related information that describes its dynamic nature is missing and not utilized in glaucoma management. For instance, GAT acquired during office visits may miss IOP peaks in up to 60% patients[2,3]. This may be a reason for some glaucoma patients to have progressive visual field loss in spite of apparent IOP control as measured by GAT[2,3].

A number of approaches have been investigated to provide a more comprehensive assessment of IOP dynamics. These include multiple measurements at a single office visit, self-tonometry, and IOP monitoring in sleep laboratories[4,5,6]. The utility of these approaches has been limited by the significant effort required in IOP measurement by patients and/or physician.

Twenty-four hour monitoring of IOP-related patterns with a contact-lens sensor (CLS) (Triggerfish; Sensimed AG) was introduced to fulfill the need for noninvasive continuous IOP measurement[7].The CLS detects changes in ocular dimensions associated with IOP fluctuation, and converts them into outputs of electronic units in millivolts. The measurements are summarized by 54 variables that are computed to describe 24-hour IOP dynamics[7]. CLS-based IOP monitoring has been well tolerated and the measurements have been reproducible[8,9,10,11]. Using a retrospective design, De Moraes and colleagues showed that certain CLS-variables, such as higher amplitude CLS readings, were associated with a faster rate of visual field progression in glaucoma patients[12]. In addition, Martin and colleagues reported that algorithms derived from machine learning on CLS-derived parameters could complement GAT in differentiating POAG patients from healthy subjects[13].

The purpose of the current study was to determine whether 24-hour CLS recording of changes in IOP-related ocular dimensions correlated with the rate of visual field progression and whether associations found in previous studies could be confirmed.

METHODS

Subjects

Participants were recruited from the Glaucoma Clinic at the Shiley Eye Institute and also from a longitudinal observational cohort (Diagnostic Innovations in Glaucoma Study, DIGS) at the Hamilton Glaucoma Center at University of California San Diego. Informed consent was obtained from all participants, and the methods were approved by the institutional review board. All methods adhered to the Declaration of Helsinki for research involving human subjects and to the Health Insurance Portability and Accountability Act. The DIGS is registered at http://clinicaltrials.gov (NCT00221897).

At each visit, subjects underwent a comprehensive ophthalmologic examination including visual acuity, slit-lamp biomicroscopy, IOP measurement using GAT, gonioscopy, dilated funduscopic examination, stereoscopic optic disc photography (Kowa WX3D, Kowa Optimed, Inc, Torrance, CA or Nidek 3Dx, Nidek Inc, Fremont, CA), and standard automated perimetry (SAP). Only subjects with open angles on gonioscopy were included. Subjects were excluded if they presented at baseline with a best-corrected visual acuity less than 20/40, spherical refraction more than ± 5.0 diopters and/or cylinder correction more than ± 3.0 diopters, or any other ocular or systemic disease that could affect the optic nerve or the visual field.

For this report, eyes only were included if they were diagnosed as primary open-angle glaucoma (POAG) with a minimum of 2.5 years of follow-up and at least three good quality SAP examinations. Eyes with POAG were defined as having open angles on gonioscopy, a glaucomatous optic disc appearance based on masked review of stereophotographs, elevated IOP (IOP >21mmHg), and reproducible visual field defects (VF) defects on at least three

consecutive VFs at baseline. A subject was considered to have POAG if glaucomatous visual field loss was present in at least one eye. Subjects with secondary causes of elevated IOP, other intraocular diseases, or other diseases affecting visual field or who were using medications known to affect visual field sensitivity were excluded.

Stereophotography

Stereoscopic optic disc photography was performed for all subjects. Digitized film and digital stereoscopic images (Kowa Nonmyd WX3D, software version VK27E, Kowa Company Ltd, Tokyo Japan, and Nidek 3Dx, Nidek Inc, Fremont, CA) were reviewed with a stereoscopic viewer (Screen-VU stereoscope, PS Mfg., Portland, Oregon, USA) by two or more experienced graders. Each grader was masked to the subject's identity and to the other test results. Details of the methodology employed to grade optic disc photographs as glaucomatous at the UCSD Optic Disc Reading Center has been previously described[14]. A glaucomatous appearance of the optic disc was defined as evidence of localized neuroretinal rim thinning or notching, localized or diffuse retinal nerve fiber layer defect, or inter-eye asymmetry of the vertical cup-disc ratio greater than 0.2.

Visual Field Testing

SAP was performed using the Humphrey Field Analyzer II (Carl Zeiss Meditec, Dublin, CA, USA) with the 24-2 Swedish interactive threshold algorithm (SITA Standard 24-2, Carl Zeiss Meditec, Inc., Dublin, CA, USA). All visual fields were evaluated by the UCSD Visual Field Assessment Center. Visual fields (VF) with more than 33% fixation losses or false-negative errors, or more than 15% false-positive errors, were excluded. The only exception was the inclusion of visual fields with false-negative errors of more than 33% when the field showed advanced disease. SAP tests were defined as normal if the mean deviation (MD) and pattern

standard deviation (PSD) were within 95% normal confidence limits and the Glaucoma Hemifield Test (GHT) was within normal limits. An abnormal SAP test was defined as a visual field with a PSD with P <0.05 and/or a GHT outside normal limits.

Other Ocular Parameters

Central corneal thickness (CCT) measurements were obtained for all patients using ultrasound pachymetry (Pachette GDH 500; GDH Technology, Philadelphia, Pennsylvania, USA). The mean of three measurements was used in the analysis. IOP readings were obtained using Goldmann applanation tonometry (Haag-Streit, Koeniz, Switzerland).

The CLS System

All patients underwent two or three sessions of 24-hour recording with a wireless CLS (Triggerfish, Sensimed, Lausanne, Switzerland). The device records IOP-related changes in ocular dimensions at the corneoscleral junction for as long as 24 hours, including during undisturbed sleep. The embedded microprocessor converts the recorded signal into electronic output proportional to the changes in ocular dimensions. Three hundred data points are obtained over a 30-second recording period, repeated every 5 minutes. Detailed description of wireless CLS for 24-hour IOP monitoring is available elsewhere[15]. All three sessions of CLS recordings were performed during the follow-up period between the first and last visual field testing. CLS parameters in this study is described in eAppendix 1.

Data Analysis

Rate of mean deviation (MD, decibels per year) is calculated as the slope of linear regression between MD and time (years). Univariate linear mixed-effects models were used to determine rates of VF MD progression over time and their association with CLS variables.

Multivariable models included the potential confounding factors age, MD at baseline, number of IOP-lowering medications, number of laser trabeculoplasty, number of glaucoma surgery, and CLS variables if the P value was <0.1 in univariate analysis. Collinearity of the CLS parameters included in the final model was assessed using variance inflation factor (VIF) and only parameters with a VIF less than 3 were included in the study.

Statistical analyses were performed with commercial software packages Stata 13.1; StataCorp, College Station, Texas; and R (version 3.1.0).

RESULTS

Study Population

Baseline demographic and ocular characteristics are summarized in Table 1. Thirty-two eyes of 32 POAG patients were included in this study. Baseline mean age (± standard deviation) was 69.8 ± 13.6 years. Sixteen patients (50.0%) were women. The average number of SAP examinations was 11.6 ± 5.6 (4 ~ 25). 5.1 ± 3.1 SAPs, on average, were acquired prior to CLS recordings over 3.1 ± 2.1 years, and 6.8 ± 4.2 SAPs over 2.7 ± 1.2 years following CLS recordings. The average rate of MD progression was -0.2 ± 0.4 dB/year. MD in 26 eyes progressed less than -0.5db/year, whereas 6 eyes progressed more than -0.5 db/year. The average number of glaucoma medications was 1.2 ± 1.0 and average number of laser trabeculoplasty procedures was 0.4 ± 0.7 (0 ~ 2). Six eyes underwent glaucoma surgery during the follow-up period. Eleven eyes received cataract surgery during follow-up period.

Mixed-effects Analysis

Table 2. summarizes the univariate mixed-effects model to test the association between individual CLS-recorded variables as dependent variables and rate of progression as a dependent variable. Those CLS variables with a significance ($P < 0.10$) were included in a

multivariate mixed-effect model with covariates of age (per decade), MD closest to CLS recordings (per decibel), number of laser trabeculoplasty procedures, number of glaucoma medications, and number of glaucoma surgeries (Table 3). The multivariate analysis revealed that larger nocturnal variability per 10 Units recorded by 24-hour CLS was significantly correlated with faster rate (more negative in value) of MD progression (Coefficient -0.249 ± 0.112, P = 0.035). Slope (wake to sleep), a CLS variable describing the slope of a linear fit on the period ranging from 1 hour before end of sleep to 1 hour after end of sleep, was significantly associated with faster MD decline in univariate analysis (P = 0.008). However, it is not statistically significant (P = 0.334) when adjusted for covariates described above in multivariate analysis. None of other 52 CLS variables corelated significantly with rate of glaucoma progression (Table 2, 3). To identify potential collinearity among the variables included in the multivariate Mixed-effects model, we used variance inflation factor (VIF) to quantify the correlation between variables. VIF of each variable in multivariate Mixed-effects model ranges from 1.18 to 1.67 (Table 3), with an average low VIF at 1.37. As a reference, when mean IOP was tested in multivariate mixed-effect model with the same set of covariates described above, higher mean IOP was significantly associated with faster rate of progression (Coefficient -0.036 ± 0.014, P = 0.013, VIF 1.11. Table 3). However, it may not be completely appropriate to include mean IOP as a covariate in multivariate analysis because ocular dimensional changes measured by CLS recordings are intended to be used as surrogates as better alternatives to single-time IOP measurement. CLS recordings do contain some IOP-related information.

DISCUSSION

The primary goal of this study was to determine whether 24-hour CLS profiling of IOP-related ocular dimensional changes during the course of glaucoma follow-up is associated with the rate of progressive visual field loss in glaucoma. We found that larger nocturnal variability in IOP-related ocular dimensions measured by CLS correlates with faster visual field loss among

POAG patients. For every 10-unit increase in nocturnal variability of ocular dimensional change recorded by CLS, the risk of SAP MD loss is - 0.25 ± 0.11 dB/year. This finding may have clinical implications in that 24-hour CLS-based monitoring of IOP-related changes may enhance risk stratification among POAG patients.

A number of studies have shown that larger circadian IOP variations are associated with a higher risk of glaucoma progression. Using IOP tonometry for self-measurement, Asrani et al showed the patients with larger 24-hour IOP fluctuation had a greater risk of glaucoma progression[16]. A larger degree of daytime fluctuation among patients with pseudoexfoliation glaucoma was associated with the highest risk of progressive visual field loss[17]. The magnitude of long-term IOP variability is also associated with glaucoma progression as shown with post hoc analyses of Advanced Glaucoma Intervention Study (AGIS) and Collaborative Initial Glaucoma Treatment Study (CIGTS)[18,19]. However, an association between larger IOP fluctuation and glaucoma progression was not uniformly reproduced in other studies[20]. One possible explanation for this is that GAT-based IOP assessments only capture snapshots of a patient's IOP throughout the day. Moreover, nocturnal measurements with conventional methods such as GAT require sleep interruption and, therefore, modify the physiological IOP at night.

Twenty-four hour recording of IOP-related ocular dimensional changes with CLS-based technology can, in part, overcome these limitations. However, it is important to note that CLS recording does not directly measure IOP. Rather, the measurement outputs reflect the change in ocular dimensions that are not only related to IOP, but also affected by mechanical properties of ocular tissue. Larger nocturnal fluctuation in ocular dimensions may exert more severe repeated mechanical stress on retinal ganglion cell axons at the lamina cribrosa[21, 22, 23, 24]. In addition, mechanical stress on the lamina cribrosa may lead to localized disruption of connective tissue beams and embedded capillaries, possibly leading to ischemic damage to ganglion cell axons[25,26,27,28,29,30]. Susceptibility of retinal ganglion cell axons to mechanical and

ischemic damage at lamina cribrosa may be worse at night due to lower ocular perfusion pressure. By reducing the range of daytime and nocturnal IOP variation, medications such as prostaglandin analogues could potentially reduce glaucoma progression by lowering fluctuation of the IOP-related ocular dimension measurements as well as mechanical stress at the lamina cribrosa[13,31].

Our finding that a larger degree of variability in nocturnal ocular dimensional change correlates with faster visual field loss in POAG patients is consistent with results of other investigators. Hoban et al demonstrated that a larger amplitude of the CLS curve was associated with a faster rate of visual field loss among patients with normal tension glaucoma, although the association did not reach statistical significance likely due to small sample size[32]. De Moraes et al. found that specific CLS-derived variables correlated with glaucoma progression[33,12]. Specifically, larger mean peak ratio while awake was associated with faster visual field loss. In contrast, other CLS parameters, such as the number of large peaks during sleep, night burst ocular pulse frequency, and night burst ocular pulse amplitude, were associated with slower visual field loss among glaucoma patients. They concluded that specific features in ocular dimensional changes recorded with CLS may help identify patients at higher risk of visual field loss[12]. Our study did not find the associations between night burst ocular pulse amplitude and frequency and VF loss as the study by De Moraes et al. Differences in study population and analysis methods may explain our divergent findings. Night bursts frequency and amplitude, the CLS parameters in De Moraes's study that were associated with slower VF loss, describe small signals in nocturnal ocular dimensions rather than larger and longer peaks. Moreover, with this technique large variations may result from systematic experimental artifacts which can be identified as significant principal components[34].

Our study has limitations. First, the small size of the studied cohort may limit the ability to generalize our conclusions to other glaucoma patients. Second, although CLS results were not considered as part of the algorithm in clinical decision making in this cohort of patients, this is a

retrospective study, which only suggests an association between nocturnal variation of IOP-related ocular dimension changes recorded by CLS and faster glaucoma progression. However, glaucoma in patients experiencing faster visual field deterioration is more likely to continue advancing at faster rates if no changes in treatment are made.[35] Therefore, our data suggest that CLS recordings may be useful to assess the risk of future functional loss, even in situations when sufficient prior visual field information is unavailable. A prospective study with CLS recordings at baseline is needed to elucidate the utility of CLS in predicting faster glaucoma progression. Such a finding could identify patients at higher risk of vision loss and the need for more aggressive IOP-lowering treatment.

In conclusion, we found that some CLS parameters related to larger nocturnal variability of IOP-related ocular dimensional changes may correlate with faster glaucoma progression. Our findings suggest that ambulatory CLS monitoring may enhance risk stratification in clinical decision-making for glaucoma management.

Acknowledgments:

FUNDING/SUPPORT: Supported in part by National Institutes of Health/National Eye Institute grants T32 EY026590 and by an unrestricted grant from Research to Prevent Blindness (New York, NY).

Financial Disclosure: **Z. Yang**, None; **K. Mansouri**, Santen (C), Alcon (S), Allergan (S), ImplanData (C); **S. Moghimi**, None; **R.N. Weinreb**, Heidelberg Engineering (F), Carl Zeiss Meditec (F, R), Konan (F), National Eye Institute (F), Optovue (F), Allergan (C), Bausch&Lomb (C, F), Eyenovia (C), Novartis (C).

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eAppendix 1. Triggerfish Parameters Tested in the Present Study

Triggerfish parameters definition

Triggerfish parameters are computed on a smoothed profile using the PROC LOESS SAS procedure over the entire 24-hour period.

- **Aic**: Akaike information criteria of the smoothing.
- **LowessFactor**: Lowess factor used of the smoothing.
- **WakeToSleepSlope**: Slope of a linear fit on the period ranging from 1h before start of sleep to 1h after start of sleep.
- **SleepToWakeSlope**: Slope of a linear fit on the period ranging from 1h before end of sleep to 1h after end of sleep.

The following features are computed with three variants: on whole Triggerfish function (TF) profile when X = 24h, on sleep period where X = Nocturnal or on wake period where X = Diurnal.

- **X_AUC**: Area under the TF profile.
- **X_MaxPeakRatio**: Max ratio between peak height and peak duration.
- **X_MaxTroughRatio**: Max ratio between trough depth and trough duration.
- **X_MeanPeakRatio**: Mean ratio between peak height and peak duration.
- **X-MeanTroughRatio**: Mean ratio between trough depth and trough duration.
- **X_MeanVariability**: TF Variability from the mean. Calculated as TF variability around the mean value of all raw (not smoothed) TF measurements in the respective period.
- **X_MedianPeakRatio**: Median ratio between peak height and peak duration.
- **X_MedianTroughRatio**: Median ratio between trough depth and trough duration.
- **X_MinPeakRatio**: Min ratio between peak height and peak duration.
- **X_MinTroughRatio**: Min ratio between trough depth and trough duration.
- **X_PeakCount**: Number of peaks in smoothed profile.
- **X_PeakCount30min**: Number of peaks lasting less than 30 minutes in smoothed profile.
- **X_PeakCount90**: Number of peaks bigger than 90 mV eq in smoothed profile.
- **X_TroughCount**: Number of trough in smoothed profile.
- **X_Variability**: Variability around the smoothed profile calculated as follows.

Statistical features

- **Amplitude**: Amplitude of whole TF profile
- **Mean**: Mean of TF profile
- **Median**: Median of TF profile
- **Std**: Standard deviation of TF profile