24-Hour Monitoring of Intraocular Pressure Fluctuations Using a Contact Lens Sensor: Diagnostic Performance for Glaucoma Progression

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Purpose. The purpose of this study was to compare 24-hour intraocular pressure (IOP) related fluctuations monitoring between 2 groups of visual field progression rates in patients with open angle glaucoma (OAG).

Methods. Cross-sectional study performed at Bordeaux University Hospital. Twenty-four-hour monitoring was performed using a contact lens sensor (CLS; Triggerfish; SENSIMED, Etagnières, Switzerland). Progression rate was calculated using a linear regression of the mean deviation (MD) parameter of the visual field test (Octopus; HAAG-STREIT, Switzerland). Patients were allocated into two groups: group 1 with an MD progression rate <-0.5 dB/year and group 2 with an MD progression rate ≥ -0.5 dB/year. An automatic signal-processing program was developed and a frequency filtering of the monitoring by wavelet transform analysis was used to compare the output signal between the two groups. A multivariate classifier was performed for prediction of the faster progression group.

Results. Fifty-four eyes of 54 patients were included. The mean progression rate was -1.09 ± 0.60 dB/year in group 1 ($n = 22$) and -0.12 ± 0.13 dB/year in group 2 ($n = 32$). Twenty-four-hour magnitude and absolute area under the monitoring curve were significantly higher in group 1 than in group 2 (group 1: 343.1 ± 62.3 millivolts [mVs] and 8.28 ± 2.10 mVs, respectively, group 2: 274.0 ± 75.0 mV and 6.82 ± 2.70 mVs respectively, $P < 0.05$). Magnitude and area under the wavelet curve for short frequency periods ranging from 60 to 220 minutes were also significantly higher in group 1 ($P < 0.05$).

Conclusions. The 24-hour IOP related fluctuations characteristics, as assessed by a CLS, may act as a risk factor for progression in OAG. In association with other predictive factors of glaucoma progression, the CLS may help adjust treatment strategy earlier.

Keywords: glaucoma, intraocular pressure (IOP), contact lens sensor (CLS), visual field, glaucoma progression, circadian rhythm

Glaucoma is a neurodegenerative disease defined by a progressive loss of optic nerve axons and retinal ganglion cells resulting in a characteristic enlargement of the optic nerve head cup and associated visual field defects.[1] Several studies have demonstrated that the level of intraocular pressure (IOP) plays an important role in glaucoma onset or progression, even in glaucoma cases with an IOP measured in the normal range using the standard Goldman applanation tonometry.[2–8]

Despite the importance of IOP measurements in glaucoma care to preserve visual function and related quality of life, the current method of measurement could miss IOP peaks or 24-hour fluctuations and delay treatment changes. Indeed, the majority of IOP peaks occurs at night or early in the morning and thus outside office-hour limits.[9–11] Jonas et al. found that any single IOP measurement taken within office hours limits had a higher than 75% chance to miss the highest point of IOP over a 24-hour cycle.[10] Moreover, 24-hour IOP monitoring by iterative IOP measurements during hospitalization is time-consuming and expensive for a frequent use in clinical practice. Furthermore, this method of measurements cannot be performed under physiologic conditions because of the awake and standing conditions required for IOP measurements during the night period. Additionally, although the role of 24-hour IOP fluctuations in glaucoma onset or progression still remains controversial, Grippo et al. found that untreated patients with ocular hypertension who converted to glaucoma had significantly different 24-hour IOP pattern from healthy controls.[12–15] Liu et al. also found that the diurnal to nocturnal IOP profile was significantly different between early glaucoma and healthy patients.[15] Finally, in the Advanced Glaucoma Intervention Study, Caprioli and Coleman showed that long-term IOP fluctuations were associated with visual field progression in

patients with low mean IOP but not in patients with high mean IOP.[13]

Some intra-ocular and extra-ocular devices have recently been developed to estimate IOP fluctuations and provide a permanent 24-hour monitoring as a potential additional biomarker for glaucoma.[16] Triggerfish (Sensimed AG, Lausanne, Switzerland) is an extra-ocular contact lens sensor (CLS) device with a strain gauge assuming that changes in corneal curvature and circumference could be related to IOP fluctuations. This relationship was previously validated using an in vitro model of cannulated porcine eyes.[17] The CLS assumes to record IOP related fluctuations in a real-life setting for up to 24 hours including during sleep time. Published studies also showed fair to good reproducibility of the CLS 24-hour monitoring patterns without any significant serious adverse events related to the device.[18,19] Agnifili et al. found that the CLS was able to differentiate output signal patterns of glaucomatous eyes from healthy subjects with glaucoma cases exhibiting more prolonged peaks and higher fluctuations than healthy subjects.[20] Interestingly, the authors also showed different output signal patterns between healthy eyes and normal tension glaucoma eyes. Tojo et al. showed that patients with exfoliative glaucoma had a significantly larger range of 24-hour IOP-related fluctuations and an earlier acrophase than healthy subjects: all healthy eyes had their maximum CLS value during the night period, compared to only 64% of glaucomatous eyes.[21] De Moraes et al. found that the CLS output signal could be associated with the rate of progression of treated glaucomatous eyes.[22] However, despite published evidence, there is currently no consensual method for the analysis and interpretation of the CLS output signal. Given that potential bias could affect the signal recorded by the CLS, definition of discriminant features within the 24-hour output signal pattern by signal processing methods is therefore needed. Additionally, although this device could be of interest to discriminate glaucomatous eyes from healthy eyes, an early detection of patients with glaucoma with a high risk of visual field progression is also an important issue for patients in order to adjust treatment earlier. Therefore, biomarkers of early detection of glaucoma progression are scarce, particularly when IOP seems controlled, and the CLS performance for glaucoma progression has to be analyzed.

Hence, we developed an automatic method of CLS output signal processing and we conducted a study to compare the 24-hour IOP related fluctuations monitoring pattern recorded by the CLS between two groups of patients with open angle glaucoma (OAG) with different rates of visual field progression. Then, we developed a prediction model of progression based on the output signal features significantly associated with a faster rate of visual field progression obtained after the comparison of our two groups.

Materials and Methods

This was a cross-sectional prospective study performed in the department of Ophthalmology at Bordeaux University Hospital (France). The signal processing method was developed in the electrophysiology and heart-modeling institute (IHU LIRYC) at Bordeaux University (France). The aim of the study was to analyze and compare the 24-hour monitoring output signal provided by a CLS between 2 groups of patients with OAG with different rates of visual field progression measured with standard automated perimetry.

All subjects provided informed written consent for enrollment in the study. The research followed the Declaration of Helsinki's tenets and the study was approved by the institutional review board and by the ethical committee of Bordeaux in 2013. This trial is registered with ClinicalTrials.gov, number NCT01849536.

Participants

Between May 2015 and May 2016, we consecutively included patients with OAG with at least a 2-year follow-up and at least 5 reliable visual field tests. The worse eye of each patient was included.

Glaucoma was defined as a chronic neuropathy (asymmetric cup/disc ratio >0.2, rim thinning, notching, excavation, or retinal nerve fiber layer defect) with progressive changes of the visual field and reliable abnormal results.[1]

All patients underwent visual field tests using standard automated perimetry (Octopus; HAAG-STREIT, Koeniz-Berne, Switzerland) and a 30-2 dynamic strategy. Reliability of visual field was defined with false positive and false negative rates lower than or equal to 20% and with fixation losses rate lower than 10%. Glaucomatous visual field damage was defined with at least 3 contiguous test points within the same hemifield on the pattern deviation plot at $P < 0.01$, with at least 1 point at $P < 0.005$, on at least 2 consecutive examinations. All patients underwent at least 5 visual field tests over a period of at least 2 years before inclusion. Visual field progression was defined using a trend-based analysis and a linear regression was performed on the mean deviation (MD) of the visual field test to calculate a rate of progression expressed in dB/year. Then, patients were allocated into 1 of the 2 groups of glaucoma progression: group 1 for eyes having a rate of visual field progression faster than -0.50 dB/year and group 2 for eyes having a rate of progression slower than or equal to -0.50 dB/year. The threshold of -0.5 dB/year was chosen based on the approximate median of visual field progression rates of our population sample in order to define a group of fast visual field progression and a group of slow visual field progression.

Central corneal thickness (CCT) was measured using anterior segment optical coherence tomography and IOP was measured using Goldman applanation tonometry between 8:00 AM and 8:30 AM and before the CLS was placed on the surface of the eye.

We excluded patients with angle closure or secondary glaucoma, except exfoliative and pigmentary glaucoma, eyes suffering from corneal or conjunctival disease, or severe dry eye syndrome defined as severe symptoms and a tear break-up time lower than 5 seconds or corneal fluorescein staining, and eyes with history of glaucoma surgery. Eyes with unreliable visual field tests or with severe visual field damage defined by an MD value worse than 20 dB were also excluded. If both eyes were eligible, only the eye with the worse MD value was included in order to minimize the impact of the CLS wearing on daily activities.

24-Hour IOP Related Fluctuations Monitoring Using a CLS

We used a CLS with a strain gauge (Triggerfish; Sensimed AG, Lausanne, Switzerland) to assess 24-hour IOP related fluctuations monitoring for each eye included. The technology of the CLS was published by Leonardi et al.[17,23] The

strain gauge is a platinum-titanium sensing-resistive gauge that enables a recording of circumferential changes in the area of the corneoscleral junction by varying its voltage according to its deformation. A microprocessor connected to the gauge sends an output signal proportional to changes of the strain gauge's voltage. Wireless power and data transfer are achieved using a patched periorbital antenna, which is made possible by using an inductive coupling system. Two coils are coupled: the first one is a gold coin connected to the strain gauge into the contact lens, and the second one is a copper coil inserted into the patched periorbital antenna. A cable connects the periorbital antenna to the portable recorder, which contains the battery that powers the device. The contact lens is made in silicone because of its oxygen permeability and water absorption making it insensitive to the hydration level at the ocular surface. To render silicone hydrophilic and thus achieve proper fitting conditions of the lens on the eye, the contact lens surface is treated with oxygen plasma. The CLS exists in three different base curves to fit a large range of corneas. CLS adaptation was performed according to the manufacturer's recommendations.

The CLS takes a measurement every 5 minutes (i.e. a total of 288 measurements for a 24-hour recording). Each measurement is composed of 300 samples of the voltage corresponding to the deformation of the corneoscleral junction during 30 seconds (10 Hz sampling rate). The CLS standard analysis reports the median value over each 30 second measurement, the output values are voltages expressed in millivolt (mV).

Each monitoring started between 8:00 AM and 8:30 AM following Goldman applanation tonometry IOP measurement and the CLS was removed 24 hours later.

Signal Processing

A three-step dedicated signal processing method was developed and implemented under MATLAB software (Mathworks, Natick, MA, USA). Sensimed (Lausanne, Switzerland) provided the raw outputs of the CLS data for each patient: 300 samples during 30 seconds every 5 minutes during the 24 hours ($N = 86{,}400$ samples). The company was masked to clinical data.

First, blinking artifacts were removed from the signal. During the day period, the 30-second periods are regularly distorted with abnormal high values that last for about 10 milliseconds. These outlier areas were identified as being associated with blinking movements (Fig. 1B during the day period, and Fig. 1C during the night period). An adaptive threshold-based derivative method was developed to automatically detect these areas and linear interpolation was performed to smooth the signal.

A positive voltage difference between the first values of the recording and the last values 24 hours later was observed in almost all recordings. Assuming that circadian biorhythms are endogenous, 24-hour oscillations of the physiological systems, including sleep/awake cycles, metabolic, or cardiovascular 24-hour activities, cell cycles, and 24-hour supranucleus brain activities, the positive trends were compensated by a linear interpolation between the first 5 minutes of the recording and the last 5 minutes 24 hours later[24] (Fig. 2A).

Finally, a wavelet-based filtering approach was applied. This method, commonly used for biosignal analysis, decomposes the original signal into N sub-signals using a "mother" wavelet W at N scale levels (w_1 to w_N), each within a specific frequency range.[25] Table 1 shows the correspondence between each wavelet w_i and the range of frequency when using a decomposition over $N = 10$ scale levels. The

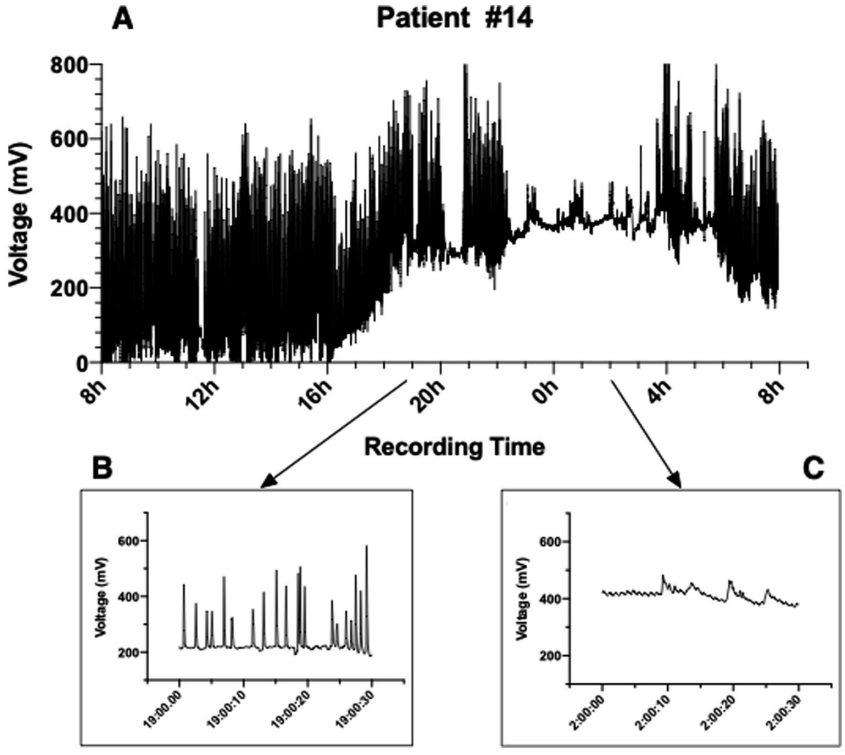

Figure 1. CLS 24-hour output signal raw data (**A**); voltage record during the day period showing recurrent high magnitude peaks associated with blinking movements (**B**); voltage during the night period without recurrent high magnitude peaks (**C**).

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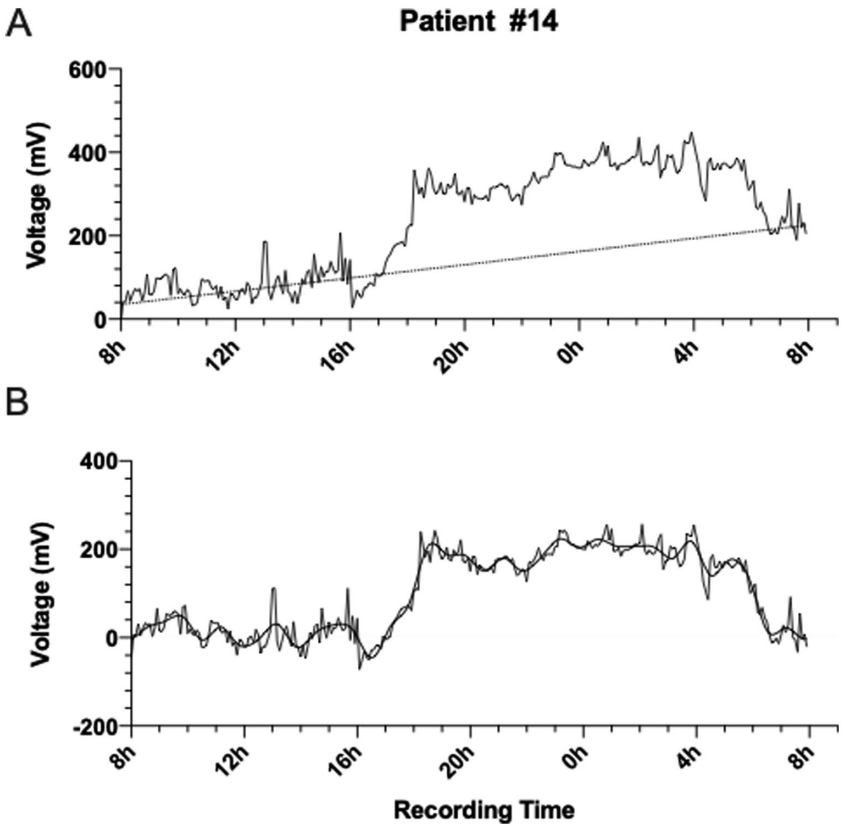

Figure 2. Signal processing steps with MATLAB R2017b (Mathworks, Natick, MA, USA): main curve of the monitoring made by the median of each 30 seconds period after removing of blinks outliers (*black line*) (**A**); linear regression applied to the entire monitoring (*dashed line*), and frequency filtering of the monitoring by wavelets decomposition (*bold black line*) (**B**).

Table 1. Characteristics of the Frequency Content of Wavelet Transform Used for the Frequency Filtering of the Contact Lens Sensor Output Signal

	Frequency Content (Min)	
Wavelet	**Minimum**	**Maximum**
W_1	10	30
W_2	20	70
W_3	30	125
W_4	60	220
W_5	120	500
W_6	220	1000
W_7	500	2000
W_8, W_9, and W_{10}	≥800	≥4000

decomposition of the signal on each wavelet w_i allows the analysis of the corresponding frequencies contained in the signal (Fig. 2B).

Output Signal Features

We defined two sets of features to assess IOP fluctuations. The first set was related to long-term fluctuations in IOP and aimed to differentiate between day and night periods; the second set was related to more rapid fluctuations in IOP (peaks of IOP).

Features belongings to the first set were calculated on the sub-signal that lied in the frequency range of diurnal fluctuations (cumulative decomposition from W_4 to W_{10}). Two features were computed (Fig. 3A):

- The diurnal amplitude, which is the highest voltage magnitude of the curve over the 24-hour period of the monitoring (called h24Magn, expressed in Volt [V]).
- The absolute area under the monitoring curve (h24Area, expressed in Volt.second [Vs]).

IOP related to more rapid fluctuations (ultradian rhythm) were computed on the two sub-signals obtained from the decomposition on w_4 and w_5 corresponding to fluctuation of period 60 to 220 minutes, and 120 to 500 minutes, respectively. Two features per decomposition were computed (Fig. 3B):

- The magnitude of the sub-signal from w_4 decomposition: w4Magn and w5Magn, expressed in V.
- The absolute value of the area under the curve of sub-signal from w_4 decomposition (w4Area) and from w_5 decomposition (w5Area) expressed in Vs.

Classification Between the Two Groups

The objective being to design a classifier that allows the automatic classification of the patients group 1 versus group 2: classification accuracy of each feature presented above used individually (univariate classification) was tested and reported as the area under the curve of the corresponding receiver operating curve (AUROC).

Then, a multidimensional classifier (multivariate classification) based on linear discriminant analysis was optimized to account for several features simultaneously: a

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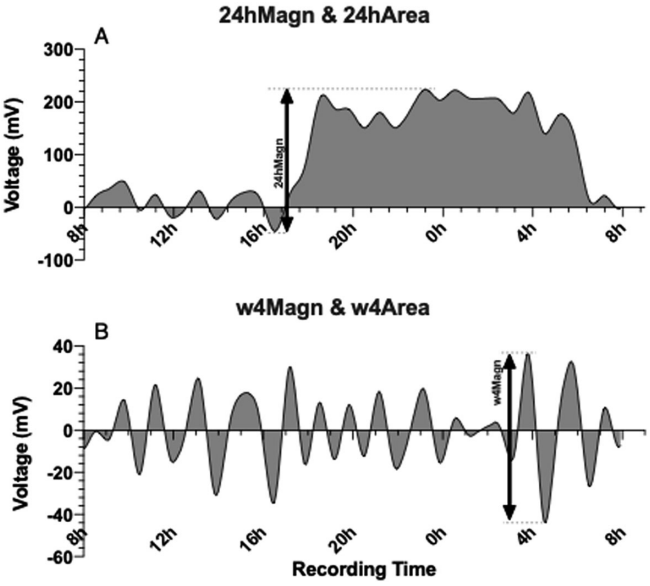

Figure 3. Output signal after signal processing and features generated for analysis. (**A**) Maximum magnitude (24hMagn) is indicated by the *arrow*, absolute area under the monitoring curve (24hArea) for 24-hour fluctuations appears in *grey*; (**B**) Maximum magnitude (w4Magn) is indicated by the *arrow*, absolute area under the sub-signal from the decomposition over the wavelet w_4 (w4Area) for fluctuations of frequency period ranging from 60 to 220 minutes appears in *grey*.

20-fold cross-validation strategy was used to divide the database into training sets and validation sets. The training sets were used to perform (i) feature selection and (ii) classifier parameter fitting. The results are presented on the validation sets. Feature selection was performed using the statistics-based method of machine learning presented by Stoppiglia et al. that orders the available features according to their contribution to a multivariate classifier.[26] All available demographic, ophthalmological, and wavelets features of the output signal were included in the model.

Outcomes

The primary outcome was to compare the mean values of the features we selected from the 24-hour monitoring raw output signal recorded by the CLS between group 1 and group 2.

The secondary outcome was to analyze the diagnostic performances of our features to discriminate the two groups of patients with OAG. Finally, we performed an internal validation of our results and defined a score based on the performance of all the features to discriminate the output signal patterns of the two groups.

Statistical Analysis

Data are expressed as mean ± standard deviation (SD) or median (upper quartile–lower quartile). Qualitative variables were described using number of occurrences. Significance of differences between group 1 and group 2 was performed using a Student *t*-test, or a Mann-Whitney test for non-normal distribution. Frequencies were compared using chi-square tests.

The performance of each parameter was assessed using the receiver operating characteristic (ROC) curve method for each parameter.

Statistical analysis was performed using GraphPad Prism software version 5 (GraphPad Software Inc., La Jolla, CA, USA). Statistical significance was defined as $P < 0.05$.

Results

Fifty-four eyes of 54 patients were included in the analysis. All raw data of the 24-hour IOP related fluctuations by the CLS were complete and available. Twenty-two eyes were allocated into group 1 and 32 eyes were allocated into group 2.

Demographic and ophthalmological characteristics of the population sample are shown in Table 2. Of the 54 patients, 27 patients were women and 27 were men. The mean age was 68.5 ± 6.0 years and was not significantly different between the 2 groups. Mean IOP before the CLS placement was 15.9 ± 3.1 mm Hg and was not significantly different between the 2 groups. The mean number of visual field tests available before the inclusion was 7.7 ± 2.3 and was also not significantly different between the 2 groups. The mean rate of progression was significantly faster in group 1 than in group 2 (−1.09 ± 0.60 dB/year and −0.12 ± 0.13 dB/year, respectively; $P < 0.0001$). The severity grade of glaucoma assessed by the visual field was higher in group 1 than in group 2 with MD value of −10.57 ± 6.97 dB and −5.43 ± 4.32 dB, respectively ($P < 0.01$). The mean CCT was significantly thinner in group 1 than in group 2 (511.9 ± 20.9 µm and 533.8 ± 22.7 µm, respectively; $P < 0.05$). No serious adverse events were reported in this study.

Table 3 shows the comparison of output signal features between the two groups. During the 24-hour period, the magnitude of monitoring curve (24hMagn) was significantly higher in group 1 (343.1 ± 62.3 mV) than in group 2 (274.0 ± 75.0 mV; $P = 0.0027$), as well as the absolute value of the area under the monitoring curve (24hArea; $P = 0.0251$). When analyzing short-term periods, the sub-signal decomposed on the wavelet with a frequency content ranging from 60 to 220 minutes exhibited a significantly higher magnitude (w4Magn) in group 1 (110.1 ± 33.4 mV) than in group 2 (86.1 ± 21.7 mV; $P = 0.0316$), as well as the absolute value of the area under the curve (w4Area; $P = 0.0188$). There was no significant difference between the two groups for the other wavelet features generated by the frequency filtering analysis.

Figure 4A shows the correlation matrix of 24-hour and wave 4 output signal features, CCT and IOP. We observed a very low positive correlation between IOP and the output signal features ranging from 0.02 to 0.13 and a very low negative correlation between CCT and the output signal features ranging from −0.22 to −0.14.

The univariate discriminative power of each feature was evaluated using the AUROC. The highest AUROC value was observed for the 24-hour amplitude parameter 24hMagn (0.739; 95% confidence interval [CI] = 0.605 to 0.872) followed by 24hArea (0.680; 95% CI = 0.534 to 0.827), W4Magn (0.673; 95% CI = 0.525 to 0.821) and W4Area (0.689; 95% CI = 0.543 to 0.835) features. The AUROC for CCT was 0.694 (95% CI = 0.554 to 0.833).

Among all available demographic, ophthalmological, and wavelets parameters, the feature selection process

Table 2. Baseline Demographic and Ophthalmological Characteristics Between the Group of Visual Field Mean Deviation Progression Rate ≤0.5 dB/Year and the Group of Visual Field Mean Deviation Progression Rate >0.5 dB/Year

Characteristics	Total (n = 54)	Group 1 MD Progression Rate <−0.5 dB (n = 22)	Group 2 MD Progression Rate ≥−0.5 dB (n = 32)	P Value*
Mean age, y (SD)	68.5 (6.0)	69.6 (6.2)	67.7 (5.8)	0.24
Gender - male subjects (%)	27 (50)	14 (63.6)	13 (40.6)	0.17
Mean IOP (mm Hg) (SD)	15.9 (3.1)	15.7 (2.74)	15.1 (2.7)	0.56
Mean CCT (µm) (SD)	525.3 (24.2)	511.9 (20.9)	533.8 (22.7)	**0.015**
MD (dB) (SD)	−7.47 (5.85)	−10.57 (6.97)	−5.43 (4.32)	**0.0072**
Mean rate of visual field progression (dB/y) (SD)	−0.52 (0.47)	−1.09 (0.60)	−0.12 (0.13)	**<0.0001**
Number of visual field tests (SD)	7.7 (2.3)	8.3 (2.3)	7.2 (2.2)	0.08

CCT, central corneal thickness; dB, decibel; IOP, intraocular pressure; MD, mean deviation; SD, standard deviation.
* Results in bold are statistically significant.

Table 3. Comparison of 24-Hour Contact Lens Sensor Output Signal Characteristics Between the Group of Visual Field Mean Deviation Progression Rate ≤0.5 dB/Year and the Group of Visual Field Mean Deviation Progression Rate >0.5 dB/Year Using Frequency Filtering and a Wavelet Transform Analysis

CLS Output Signal Characteristics	Total (n = 54)	Group 1 MD Progression Rate <−0.5 dB (n = 22)	Group 2 MD Progression Rate ≥−0.5 dB (n = 32)	P Value*
24-h characteristics				
24hMagn (mV) [mean (SD)]	302.2 (79.1)	343.1 (62.3)	274.0 (75.0)	**0.0027**
24hArea (10^3Vs [mVs]) [mean (SD)]	7.42 (2.55)	8.28 (2.10)	6.82 (2.70)	**0.0251**
Ultradian characteristics				
w4Magn (mV) [mean (SD)]	95.8 (27.7)	110.1 (33.4)	86.1 (21.7)	**0.0316**
w4Area (10^3Vs [mVs]) [mean (SD)]	1.10 (0.28)	1.24 (0.30)	1.01 (0.23)	**0.0188**
w5Magn (mV) [mean (SD)]	100.9 (38.2)	108.7 (46.2)	95.6 (31.9)	0.57
w5Area (10^3Vs [mVs]) [mean (SD)]	1.38 (0.44)	1.40 (0.45)	1.37 (0.44)	0.85

24hArea, absolute area under the monitoring curve; w5Area, absolute area under the wave; CLS, contact lens sensor; mV, millivolt; SD, standard deviation; Vs, Volt.second.
* Results in bold are statistically significant.

for the multivariate classifier led to the selection of 4 features (24hMagn, 24hArea, W4Magn, and W4Area) from the wavelet analysis, as well as the CCT parameter. In this 5-dimensionnal input space, the multivariate classifier performances over the testing sets were as follows: accuracy of 77.7% (n = 42 eyes), sensitivity of 81.3%, and specificity of 72.7%. The AUROC value of the classifier was 0.730 (95% CI = 0.583 to 0.874; Fig. 4B).

Discussion

We demonstrated that the 24-hour output signal pattern recorded by the CLS was different between patients with OAG with an MD rate of progression slower than or equal to −0.5 dB/year and patients with OAG with an MD rate of progression faster than −0.5 dB/year. Although IOP measurements performed just before CLS measurements were similar between the two groups of visual field

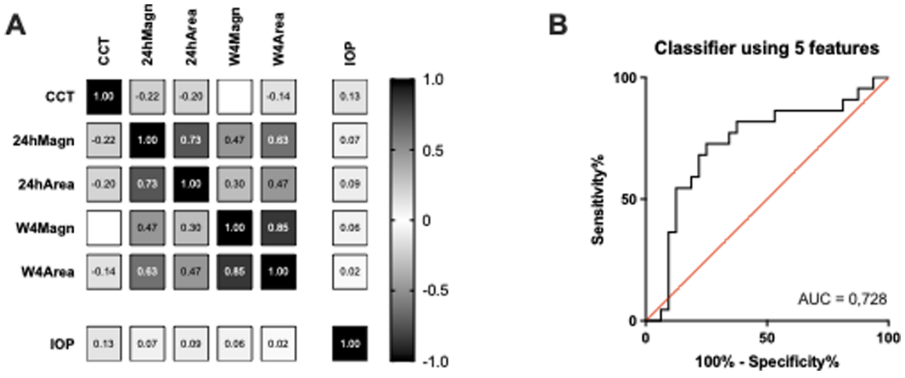

Figure 4. Correlation matrix showing the correlations between 24-hour maximum magnitude (24hMagn), 24-hour absolute area under the monitoring curve (24hArea) and wavelet w_4 maximum magnitude (w4Magn), wavelet w_4 absolute area under the monitoring curve (w4Area) features of the output signal with central corneal thickness (CCT) and intraocular pressure (IOP) (**A**); area under the receiver operating characteristic curves (AUC) of the multivariate classifier (**B**).

progression, we found differences on the shape of wavelets with short frequency periods as well as on the shape of the curve over the 24-hour period. Whereas the amplitude and the absolute area under the monitoring curve were significantly higher in the group of faster rate of progression over the 24-hour period, particularly at night, we also found that the amplitude and the absolute area under the monitoring curve on shorter frequency periods ranging from 60 to 220 minutes were significantly higher in this group of patients with OAG.

Although the exact interpretation of the output signal pattern is still controversial, we speculate that the higher mean values of amplitude and absolute area under the curve we observed during the 24-hour period for the group of faster rate of visual field progression could be related to a higher and more prolonged night increase in corneal curvature and circumference as measured with the CLS. Additionally, our results are consistent with previously published results.[20–22,27–30] Indeed, De Moraes et al. also analyzed the output signal provided by the CLS on a cohort of 40 patients with glaucoma with a progression of the visual field.[22] By using a different methodology of signal processing, they also observed that the output signal had a different shape for patients with a faster rate of visual field progression. They reported a higher number of long peaks and higher mean peak ratio when patients were awake. Tojo et al. also showed that high maximum amplitudes over the 24-hour period as well as during the night period were associated with a higher risk of visual field progression in glaucoma patients.[30] Finally, Martin et al. showed higher values of several features of the output signal features using machine learning methods in a large cohort of patients with OAG compared to control patients.[28]

To evaluate short-term IOP related fluctuations (IOP peaks), we developed an original method of automatic signal processing based on a frequency filtering of the monitoring by wavelet transform. This method enables a detection of diurnal changes within the 24-hour period (ultradian biorhythm) using a wide range of frequencies. Interestingly, we found that signal amplitude and area under the curve of wavelet at periods ranging from 60 to 220 minutes were significantly higher in the group of patients with OAG with a faster rate of progression. These higher in amplitude and longer changes in corneal curvature or circumference observed in this group of patients with OAG could be related to short term IOP peaks, which may be associated with a higher risk of visual field progression. Although they used a different methodology of output signal analysis, De Moraes et al. also showed short-term changes in the output signal of patients with glaucoma.[22] Indeed, they observed that the amplitude and the length of short-term peaks were associated with a faster rate of visual field progression. As short-term IOP peaks characteristics are not a priori known, our method of signal processing using a wavelet decomposition on a wide range of frequency periods could enable a more reproducible and accurate analysis of the raw output signal provided by the CLS. Hence, daily short-term IOP peaks, particularly peaks ranging from 60 to 220 minutes may play a role in glaucoma progression and the analysis of such IOP peaks could act as a biomarker to help predict the risk of visual field progression. However, our findings would need to be confirmed in other clinical and experimental studies.

A strength of our study was to analyze raw data of the output signal in order to limit measurement bias and improve the accuracy of the 24-hour monitoring provided by the CLS in patients with OAG. First, by removing recurrent outliers of the output signal only observed during the day period that are very likely related to blinking, we hypothesize our method should have limited measurement bias and the comparison between the day and night periods. Indeed, these data points had very high values for a very short period of time. Instead of the removal of these outliers, the Triggerfish software uses the median of these measurements in the final analysis. Thus, we speculated that this processing method of data points could bias the measurement of change in corneal curvature or circumference during the 24-hour monitoring by overestimating the amplitude and length of peaks particularly during the diurnal period. Furthermore, these outliers could also bias the comparison of the output signal between the day and night periods. Second, as expected during a 24-hour monitoring, diurnal changes in corneal curvature or circumference should follow a circadian biorhythm.[24] Thus, as the difference between the beginning and the end of the monitoring may overestimate the area and the amplitude of the output signal pattern recorded during the night period, we chose to compensate this difference by applying a linear regression to the entire monitoring. Although the origin of this difference is controversial, we assumed that this difference may be due to a measurement bias. Indeed, Hubanova et al. showed a significant increase in CCT following the 24-hour wearing of the CLS on the studied eye as compared with the fellow control eye of the same patient.[31] However, the authors could not conclude whether changes in CCT observed during CLS wearing could significantly modify the corneoscleral junction angulation and influence the shape of the output signal at the end of the monitoring. Finally, to our knowledge, we were the first to apply a method of wavelet transform on the raw output signal to optimize information recorded during the 24-hour period. Indeed, this method is usually carried out in diurnal rhythm analysis to detect changes within the 24-hour period at progressing frequency periods from shortest periods to the 24-hour period.[25] This method of signal processing also provides a smoothing of the signal to overcome the noise commonly observed in such monitoring. Interestingly, we also observed a very weak correlation between analyzed output signal features and IOP or CCT parameters. Thus, we speculate the influence of IOP or CCT on the amplitude and area of the 24-hour period and wavelet 4 features is likely weak. Hence, we believe the method of signal processing we used in our study can have standardized and optimized the analysis of short-term changes in corneal curvature and IOP-related fluctuations in our cohort of patients with OAG.

Although we found a significant difference of output signal patterns between the group of patients with OAG with a faster visual field progression and the patients with OAG group with a slower visual field progression, the diagnostic performance of the CLS to discriminate our two groups was moderate. However, our findings are in accordance with published results on diagnostic performance of the CLS to discriminate glaucoma from healthy eyes. Indeed, in a cohort of 435 subjects, Martin et al. observed a mean AUROC value of 0.611 with a best value at 0.759 using machine learning methods to analyze the CLS output signal pattern.[28] First, the moderate diagnostic performance of CLS could be related to the role played by IOP fluctuations in glaucoma onset or progression, which is not fully understood. Indeed, pathophysiology of glaucoma is multifactorial and besides IOP, some other factors could play an independent or an additive role to the progressive death of retinal ganglion cells, as blood supply around the optic nerve head,

biomechanical properties of lamina cribrosa, or altered neuronal functionality of these cells.[1] Then, the diagnostic performance of the CLS we observed could also be related to the threshold of −0.5 dB/year we chose to define our 2 groups of visual field progression. Although there is no consensus in the literature to define a fast rate of visual field progression, we chose the threshold of −0.5 dB/year because it was approximately the median of rate of progression of our population sample. In comparison, Heijl et al. reported a mean progression rate of -0.8 dB/year and a median progression of −0.62 dB/year.[7] Chauhan et al.[32] reported on a cohort of 2324 patients in which approximately a quarter of the eyes had a rate of progression of −0.30 dB/year or higher and they selected the threshold of −1 dB/year to define fast progressors. Boodhna et al. reported on a cohort of 18,926 eyes in which approximately a quarter of the eyes had a visual field progression higher than −0.51 dB/year.[33] Hence, as there is no described specific biomarker to help predict visual field progression below −0.5 dB/year, we speculated that the monitoring of IOP-related fluctuations could be of interest in current practice for this category of patients with OAG to help adjust treatment strategy earlier. Additionally, despite moderate diagnostic performance of the CLS to discriminate the patients with OAG with a progression rate slower than or equal to −0.5 dB/year from patients with OAG with a rate of progression fast than −0.5 dB/year, the score we developed and tested using a sensitivity analysis strengthened our findings. Indeed, the performance of the score was fair in our population sample and this score could help define a predictive model of glaucoma progression. Hence, in association with other risk factors of glaucoma progression, the signal provided by the CLS may help predict the risk of glaucoma progression in current practice.

Our study may have some limitations that need to be considered. First, we chose to define glaucoma progression using a standard automated perimetry and a trend-based analysis with a linear regression of the mean deviation of visual field tests.[34] Retinal sensitivity values measured with standard automated perimetry could fluctuate for the same eye with increasing test-retest variability with decreasing retinal sensitivity values across the retina.[35] Furthermore, glaucoma progression can also be assessed using an event-based analysis of the visual field.[34] However, the trend-based analysis approach is commonly used in published studies analyzing glaucoma progression and also provides a rate of progression useful to analyze characteristics of glaucoma on a long-term period.[2,8,36] Furthermore, eyes were eligible when at least 5 reliable visual fields were performed over at least a period of 2 years and the mean number of visual field was 7.7 ± 2.3 in our population sample. At the beginning of standard of care follow-up visits, patients were classified as suspect of glaucoma progression on the visual field and progression was later confirmed with time and additional visual fields. Thus, we hypothesize that the rate of progression of our population sample was reliable and that our findings could be applied to such population groups. Another potential limitation could be related to the device we used to evaluate IOP related fluctuations and the potential bias that could be associated with this technology. Indeed, the 24-hour monitoring provided by the CLS measures the changes in corneal curvature and circumference expressed in voltage and thus does not provide real IOP measurements. Voltage measured with the strain gauge is supposed to be modified by changes in corneal circumference at the corneoscleral junction and the correlation between volumetric changes and IOP is not fully established. Hence, the correlation between voltage and IOP related fluctuations still remains unclear.[37,38] Whereas Mansouri et al. found that the coefficient of correlation between CLS and pneumatonometer was $R^2 = 0.914$, Vitish-Sharma et al. found that the mean correlation coefficient between CLS output signal measurements and IOP measurements was $r = 0.291$.[39,40] Additionally, the association of corneal parameters as corneal thickness at the corneal junction and CLS measurements or the influence of a 24-hour wearing of the CLS on the cornea could also influence the recorded CLS output signal particularly at the end of the monitoring.[29,31] In our population sample, we observed a 20-µm difference in mean CCT measurements between the two groups at baseline. Although the CLS measures the changes in corneal curvature or circumference at the corneal junction and not at the apex of the cornea, the influence of this difference in central corneal thickness on our results remains unclear. However, the score we calculated took into account central corneal thickness parameter and was still able to discriminate the two groups of progression. Finally, although our multivariate classifier model showed good diagnostic performances to diagnose OAG with a faster rate of progression, this classifier would also need to be tested in an independent and larger population sample to confirm or refine its diagnostic performances (external validity analysis) and enable generalization of findings.

In conclusion, we found significant difference of 24-hour as well as short-term IOP related fluctuations characteristics as assessed by a CLS and an automatic signal processing of the output signal between patients with OAG with rates of visual field progression slower than or equal to −0.5 dB/year and patients with OAG with rates of visual field progression faster than −0.5 dB/year. In association with other predictive factors of glaucoma progression, these CLS features could act as additive risk factors in clinical practice and help adjust treatment strategy earlier. However, further studies are still needed to confirm our findings – particularly the role of short-term IOP peaks in glaucoma progression – and strengthen the association between IOP fluctuations and CLS measurements as well as the influence of corneal parameters on CLS measurements.

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