Monitoring Vigilance during Perimetry by Using Pupillography

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PURPOSE. To report and present data on a method for monitoring patient vigilance during a visual field test by using pupillography.

METHODS. Pupil diameter was recorded at 60 Hz with an eye movement tracking system in 13 patients attending the glaucoma outpatient clinics at Manchester Royal Eye Hospital. The patients were instructed to fixate a central target and to press a response button whenever they saw a stimulus that was randomly presented 5° to the left or right of fixation. A repetitive up/down bracketing strategy was used (1-dB steps, 2-second interstimulus intervals, 10-minute duration) at these two locations. Wavelet analysis was used to extract a denoised measure of the pupil diameter and the amplitude of any pupillary fatigue waves. The relationship between the probability of seeing a stimulus and these two components of the pupil response was investigated.

RESULTS. Good pupil data were obtained from 12 patients. Most (8/12) showed gradual miosis and periods of pupillary fatigue waves during the recording session. Pupillary fatigue became more evident with test duration, and the probability of seeing a stimulus was higher when the pupil was dilated (P < 0.001) and the amplitude of the papillary fatigue waves was low (P < 0.001).

CONCLUSIONS. Pupil miosis and fatigue wave amplitude are related to vigilance in patients who take a perimetric-type test. Pupillography can be used to investigate vigilance and how it contributes to perimetric variability. (Invest Ophthalmol Vis Sci. 2010;51:3540–3543) DOI:10.1167/iovs.09-4413

Over the past 20 years, several important advances have been made in perimetric procedures. Examination times have been reduced,¹ and new data analysis tools have improved clinical decision-making.¹² However, current techniques still show large amounts of test–retest variability. With the current levels of variability, accurate estimates of the rate of progression, which are important in appropriate and effective management of glaucoma, require amassing large amounts of data, placing a considerable burden on ophthalmic services.²,⁵

Most threshold visual field tests require patients to press a response button, whenever they see one of a large number (~200) of sequentially presented stimuli, many of which are close to their threshold. Most of the patients find the process, which takes 5 to 8 minutes to complete for each eye (SITA standard, 24-2).⁴,⁵ very exhausting⁶ and commonly report difficulty in maintaining vigilance and attention. Vigilance and attention are two terms widely used in the literature to describe the activation status of the cortex—others being arousal and alertness.⁷ Vigilance will be used throughout this article, as it implies sustained attention and therefore better describes the demands of a visual field test.

Vigilance describes a degree of arousal on the sleep–wake axis, and there is a well established relationship between pupil dynamics and sleepiness.⁷ In early work, Lowenstein et al.⁸ and Ludtke et al.⁹ observed that, when sleepy individuals are placed in the dark, their pupils dilate and then, after a brief period, become increasingly miotic. In addition to miosis, the pupils often begin to slowly oscillate in size, with frequencies <0.8 Hz and amplitudes that can exceed 1 mm. These oscillations are known as pupillary fatigue waves, and their occurrence has led to the development of a pupillographic sleepiness test (PST) which involves the monitoring of pupil dynamics for 11 minutes after the patient has been placed in the dark. Several methods have been developed to quantify the results from the PST. One of these is the pupillary unrest index, which is the integrated sum of slow movements during the dark period. Wilhelm et al.¹⁰ have shown that this index correlates well with other objective (EEG) and subjective (e.g., Stanford Sleepiness Scale) measures of sleepiness in normal subjects.¹⁰,¹¹ Lowenstein et al.⁸ have also shown that older persons tend to show these pupil effects sooner and have more frequent periods of pupillary fatigue waves.

In the dark, pupil size is primarily determined by changes in the activity of the sympathetic nervous system, and sympathetic nervous activity changes with the level of sleepiness. In the light, there is increased activity from the parasympathetic nervous system, which responds to light levels and accommodation.⁸ Research into sleep and sleep disorders has therefore concentrated on developing techniques based on measures taken in the dark. However, the types of pupillary movements that occur in sleepy individuals when they are placed in the dark also occur in the light when subjects are presented with monotonous repetitive tasks.¹²,¹³ Nishiyama et al.¹² observed miosis and pupillary fatigue waves in subjects undertaking an uneventful driving simulation. They were also able to show that during periods when pupillary fatigue waves were present, which occurred in 80% of subjects during the 10-minute recording session, there was an increase in the frequency of missed targets and a reduction in the velocity of saccades—evidence of reduced vigilance.

In this study, we investigated how pupils vary during a perimetric-type test and report on the relationship between pupil dynamics (pupil diameter and fatigue waves) and the probability of seeing a near-threshold stimulus.

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Supported by the Manchester Academic Health Sciences Centre (MAHSC) and the National Institute of Health Research (NIHR) Manchester Biomedical Research Centre.

Submitted for publication October 1, 2009; revised December 21, 2009, and January 22, 2010; accepted February 11, 2010.

Disclosure: D.B. Henson, None; T. Emuh, None

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METHODS

Pupil Measurement
The pupil diameter of the test eye was measured with a high-speed video eye tracker (VET; Cambridge Research Systems, Cambridge, UK) at a sampling rate of 60 Hz. This system captures images of the eye through a large dichroic mirror placed in front of the patient’s eyes and inclined at 45° to the vertical. With this arrangement, the patient has an uninterrupted visual field in excess of 30° in all meridians.

Stimulus
Stimuli (white; 0.5°; 200 ms) were presented on a 22-in. display monitor (Diamond Pro 2070; Mitsubishi, Tokyo, Japan) placed 330 mm from the patient’s eye. The display was controlled with a stimulus generator (Visage System; Cambridge Research Systems, Cambridge, UK) and custom software. The nontested eye was occluded, and any necessary refractive correction for near vision was placed in front of the test eye. After calibration, the patients were asked to fixate a central cross and to press a response key when they saw another stimulus. Stimuli were presented for 200 ms, 5° to the right or left of fixation (the location was randomized), on a background luminance of 10 cd/m². The intensity of each stimulus followed a repetitive up/down staircase strategy with a step size of 1 dB. Data were collected for 10 minutes, with an interstimulus interval of 2 seconds. All measurements were taken in a quiet room, and the patients were told that, unless something went wrong, they would not be spoken to during the test. The patients were instructed to keep fixating the central cross and to try to remain as alert as possible. The researcher remained in the room during the test.

Patients
Thirteen patients (four men, nine women; mean age, 71 years; range, 51–88) with or suspected of having glaucoma took part. They were consecutively recruited from the IOP Phasing Clinic at Manchester Royal Eye Hospital. The only exclusion criteria were unwillingness to give informed consent and recorded visual field loss that was likely to affect the two test locations (measured with HFA, SITA standard perimetry; Carl Zeiss Meditec, Dublin, CA). All patients had prior experience of threshold visual field testing. Informed, written consent was obtained from all participating patients, and the research adhered to the tenets of the Declaration of Helsinki.

Pupil Signal Processing
The raw pupil data included breaks due to blinks. These were removed by a custom algorithm that replaced the missing data with a linear fit from pre- to postblink diameters. Wavelet analysis (Reverse Biorthogonal Wavelet 3.7; Wavelet Toolbox ver. 4.1; The MathWorks, Natick, MA) was used to decompose the time-varying pupil signal into a series of components. Wavelet analysis is similar to a Fourier transform but provides information in time and frequency rather than just frequency. Although short-time Fourier transform can provide frequency information within a time window, the time information is still limited in comparison to wavelet analysis. As we were interested in detecting signals within the pupil response that may occur for only short periods, wavelet analysis was more appropriate than short-time Fourier transform of the deblinked data. The first component (approximation coefficient level 10) was the denoised pupil diameter, and the second component (detail coefficient level 8) was the low-frequency fatigue waves. Figure 1 gives three examples of the raw and extracted components of the pupil signal. To enable comparisons between patients and the computation of group findings, we calculated the percent rank of the pupil diameter and fatigue wave amplitude for each patient.

Threshold Sensitivity
The threshold sensitivity of each test location in each patient was taken as the mean test presentation intensity between 30 and 150 seconds from the start of the test. Each threshold estimate was thus based on approximately 30 up/down presentations avoiding the first few (approximately seven), to allow stabilization of the repetitive bracketing algorithm and later responses that may have been adversely affected by the loss of vigilance or fatigue.

RESULTS
Good pupil data were obtained from 12 of the 13 patients. In one patient, the pupillometer was unable to consistently track the pupil margin. In 2 of the remaining 12 patients, the upper lid began to droop during the recording session, and they had to be reminded to keep their eyes wide open.

Figure 1 gives the pupil diameter of three patients during the 10-minute recording session, along with the two wavelet components (denoised pupil diameter, which had been shifted by 0.5 mm, and fatigue wave amplitude). Figure 1a is recording from a patient whose pupil diameter started to decrease after approximately 1 minute. After 5 minutes, this patient undertook a series of long blinks that were followed by a small increase in pupil diameter, which then remained fairly stable (at just under 4 mm) for the rest of the 10-minute recording period. Also seen in this patient were pupillary fatigue waves. These were particularly noticeable between 5 and 8 minutes. The two wavelet-extracted components of the pupil signal give temporally accurate measures of the pupil diameter and fatigue wave amplitude. The second example, Figure 1b, comes from a patient who maintained an almost constant pupil diameter throughout the test, with no evidence of pupillary fatigue waves; similar responses were seen in 2 of 12 patients. The final example, Figure 1c, is of a patient who demonstrated particularly large fatigue waves after approximately 4 minutes of recording, with amplitudes reaching 0.5 mm. The amplitude of the pupillary fatigue waves showed large fluctuations that were not associated with significant changes in the denoised pupil diameter.
Figure 2 presents the median and distribution (25%–75% range) of each patient’s fatigue waves and pupil diameter for each 2-minute period of the test. The results are sequenced on the basis of the change in fatigue wave amplitude. There were considerable differences between the patients. Some showed only minor changes in the amplitude of their pupillary fatigue waves with test duration, whereas others showed marked increases. Eight of the 12 patients showed a significant ($P < 0.001$, $t$-test) decrease in their pupil diameter between the first and second 2 minutes of recording and between the first and fifth 2 minutes of recording.

To allow pooling of the data from each subject, the denoised pupil diameter and fatigue wave amplitude components of each patient were percent ranked. The probability of seeing a stimulus at a range of test intensities (3, 2, 1, and 0 dB brighter than each test location threshold) was then computed for each quintile of the percent ranked diameter and fatigue wave amplitude signals. Figure 3 gives the pooled result from all 24 test locations in the 12 patients. Combining the data from all stimulus intensities (3, 2, 1, and 0 dB above threshold) into a single regression model looking at change in the probability of being seen versus either fatigue wave amplitude or pupil diameter shows significant relationships ($P < 0.001$). The probability of seeing a stimulus declines as the fatigue wave amplitude increases or the pupil diameter decreases.

**FIGURE 2.** The median and 25% to 75% range of the fatigue wave amplitude and pupil diameter for each 2-minute period of the 10-minute test. Results from 12 patients.

**DISCUSSION**

Loss of vigilance by a patient during a visual field examination is a well-recognized problem. Patients often report difficulty in maintaining their vigilance, and perimetrists often see signs of fatigue or sleepiness during a visual field test, such as a drooping upper lid, gradual miosis and, occasionally, pupillary fatigue waves.

We have shown that the characteristic pupillary patterns of sleepiness noted by Lowenstein et al.8 in patients placed in the dark are also found in most patients when they undergo a perimetric-type test. We have also shown that two components (diameter and fatigue wave amplitude) are associated with a loss of sensitivity. These components have been shown to represent movement toward sleep on the wake–sleep axis. Although both components show a similar relationship with time (Fig. 2) and sensitivity (Fig. 3), individual traces (Fig. 1) often show rapid, transient changes in fatigue waves that are not present in the diameter component. Figure 1 also shows early miosis that is not associated with any pupillary fatigue wave. These two components thus provide independent measures of vigilance.

The two components of the pupil signal were found to change with test duration in the majority (8/12) of the patients. Hudson et al.15 reported a loss in sensitivity with test duration in a group of control and ocular hypertensive patients. The patients were examined with the Octopus G1X (Interzeag, Schlieren, Switzerland), which allows limited time segmentation of threshold estimates. They were also able to show that a brief rest period during the test gave a temporary improvement in sensitivity. The two components described in this article are both objective and have a high temporal resolving power. They can detect changes that occur for only a few seconds and thus provide an improved method of monitoring temporal changes in response characteristics during a visual field test. They can also provide evidence on how long patients can remain vigilant, which appears to be a much shorter time than even the fastest threshold algorithms.

The routine perimetric task given to patients is particularly unexciting, and one might expect that the introduction of some form of novelty could improve vigilance and perimetric performance. Li et al.16 investigated the effect of using a moving fixation target and found that it improved the sensitivity of the final threshold measures and concluded that the improvement was due to an increase in patient alertness. Pupillography could provide an objective method for assessing the benefits,
or otherwise, of including fixation shifts during a perimetric examination.

Similar improvements in both sensitivity and variability have been reported by Miranda and Henson,17 when conventional threshold testing, in which the patient presses a response button when they see a stimulus, was switched to one in which patients had to verbally report where they saw the stimuli. Again, this improvement was attributed to an increase in vigilance brought about by having to respond verbally.

De Jong et al.18 investigated whether the active presence of the perimetrist during a threshold test influences the results. The perimetrist judged alertness, fatigue, and fixation of the patient and, according to his impression, determined the speed of examination and provided psychological support. They found that there was a significant improvement in threshold repeatability with the active presence of the examiner who helped to engage the attention of the patient during the test. In two of our patients, verbal support was needed during the test to stop the upper lid from drooping and occluding the upper pupil margin. In these cases, the verbal support helped to restore vigilance.

Blink artifacts in the pupil signal were removed by linearly interpolating the pupil diameter from its size before the blink to its size after the blink. Most blinks were of a short duration (<150 ms), and this process is unlikely to have had a significant effect on the two pupil components studied. However, longer blinks may have had an effect, especially on the faster fatigue wave component. The effect on this component of removing blink artifacts would have been to reduce its amplitude and the significance of any relationship between fatigue waves and vigilance.

In this study, we used just two test locations, 5° to either side of the fixation point. This method ensured that we had sufficient data to track temporal changes in sensitivity. Routine perimetry involves the testing of far more locations extending farther into the periphery. Increasing the number of test locations may improve attention. Further work is needed to ascertain whether the changes seen in this study would still occur in patients who are performing a routine visual field test.

Most threshold test algorithms have been developed with simulations that assume patients have response characteristics (sensitivity, variability) that are invariant throughout the visual field test. The data from this study have shown that, for most patients, response characteristics are likely to deteriorate with test duration. Pupillometric findings can be used to develop better patient models for test simulations that take into account the dynamic nature of patient response characteristics. Such models are likely to show the real benefit of a further reduction in test times.

Most modern perimeters incorporate a video fixation monitor that could be used for pupillometry. The output from such a system could be used to either warn the perimetrist when the patient is becoming drowsy or modify the test algorithm in response to a loss of attention. In a similar way, pupil signals could be used to gate out data collected when vigilance is low and to provide a measure of reliability that comes from a much richer data source than that currently being used (i.e., catch trials and response times).

References