Test–Retest Variability of Multifocal Visual Evoked Potential and SITA Standard Perimetry in Glaucoma

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PURPOSE. To investigate the test–retest variability of multifocal visual evoked potential (mfVEP) and threshold perimetry in glaucoma, and to examine the relationship between the two techniques.

METHODS. Data were recorded using the AccuMap mfVEP and SITA standard program of the Humphrey Field Analyzer. Data were obtained twice within a 4-week period from both eyes of 74 patients with varying amounts of glaucomatous visual field loss. The number of defective test locations (those falling beyond a given probability value of being normal) were calculated for mfVEP and SITA, using databases incorporated within the instruments software. Reliability measures and test times were recorded along with patient test preference.

RESULTS. Both tests showed a large degree of test–retest variability in the number of defective test locations (95% limits of agreement for mfVEP and SITA being 13.39 and 9.88, respectively). A “fair to moderate” degree of spatial agreement was found between mfVEP and SITA. The number of mfVEP defective locations was dependent on the signal amplitude. No relationship was found between test–retest variability and the reliability indices for either test. The mean time taken to perform mfVEP and SITA standard was 53 and 20 minutes, respectively, and 73 of the 74 patients preferred the mfVEP test.

CONCLUSIONS. Test–retest variability was found to be slightly greater for mfVEP. The processing of mfVEP signals needs to be changed to remove the relationship between the number of defective locations and signal amplitude. The majority of patients preferred mfVEP to conventional perimetry although mfVEP takes longer to perform. (Invest Ophthalmol Vis Sci. 2004;45:4035–4040) DOI:10.1167/iovs.04-0099

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checks were white with a luminance of 146 cd/m², and the other eight were black with a luminance of 1.1 cd/m², generating a Michelson contrast of 99%. The background luminance of the screen was 73.5 cd/m². Fifty-six of the test locations were within 24° of eccentricity and the remaining two were located in the nasal region within 32° of eccentricity. The stimulus was driven at a frame rate of 75 Hz. The central area of 1° was used as a fixation target. A series of randomly changing numbers was presented at the fixation point and the patient was requested to press a button when the number 3 was seen. This was designed to enhance attention and fixation, and was used to provide indices for test reliability.

During each run, the VEP amplitudes for all the test locations were recorded for 55 seconds. EEG scaling of the VEP amplitude was automatically carried out to reduce intersubject variability. The patient was seated in a dimly lit room at a distance of 30 cm from the computer screen, with the chin slightly elevated to relax the neck muscles. A full refractive correction for near vision was worn and pupils were not dilated. Four gold disc electrodes (Grass; Astro-Med, Inc., West Warwick, RI) placed in a custom designed occipital cross electrode holder were used to permit four-channel bipolar recording. The vertical channel received information from two electrodes positioned 2.5 cm above and 4.5 cm below the inion. The horizontal channel obtained information from two electrodes located 4 cm either side of the inion. The two oblique channels received input from the lower midline electrode and either right or left horizontal electrode. The scalp was cleaned at the site of each electrode using Nuprep (D.O. Weaver and Company, Aurora, CO), and contact gel (Skintact ECG Gel; Leonhard Lang, Austria) was applied between the scalp and electrodes. The impedance of each electrode was measured with a target value of 5 kΩ or less. Raw trace data for each channel was presented in real time during each run. EEG scaling of the VEP amplitude using fast Fourier analysis is automatically carried out after each run to reduce intersubject variability. A Fourier spectrum window display is used to detect any high alpha component or electrocardiogram (ECG) contribution after each run. The analysis software incorporates a trace improvement algorithm, which is an index of the signal-to-noise ratio. The system was repeatedly run, with noisy runs replaced, until a minimum of seven good quality runs was collected from each eye.

Visual Fields

Visual field data was collected with a Humphrey Field Analyzer (Carl Zeiss Meditec) using program 24–2, SITA standard. The test was performed with the appropriate refractive correction in large aperture lenses specifically designed for perimetry. All mfVEP and visual field data were collected by the same experienced examiner. Each patient was seen twice within a 38-day period. The sequence of the two tests was randomized between patients but constant for each patient.

Analysis

The analysis was based on the number (maximum of 52 for the HFA, excluding 2 points falling within the region of the blind spot, and 58 for the mfVEP) and spatial location of the test points marked as outside of normal limits (5%, 2%, and 1%) by each instrument’s software. The mfVEP reliability indices (fixation losses [FL] and false positives [FP]) and the visual field reliability indices (FL, FP, and false negatives [FN]), were analyzed. The time taken to perform the mfVEP was recorded in a subset of patients (n = 24). To determine which test the patients preferred, all patients were asked two standardized questions by the examiner when they had completed both tests on the first visit: “Which test did you prefer?” and “Why did you prefer this test?”

RESULTS

Eighty-two patients were enrolled in the study. Six patients failed to attend both sessions and two patients were excluded.
because of poor fixation or head shaking, leaving a residual population of 74 patients (42 males, 32 females) and 148 eyes.

The mean age of the patients was 69.80 ± 10.00 years. Sixty-five were white, 7 were black, and 2 were of Asian origin. Fifty-three had primary open-angle glaucoma, 16 had normal tension glaucoma, and 5 had pseudoexfoliating glaucoma. Eyes had varying extents of visual field loss (mean deviation [MD]); mean −7.46 dB; range, +1.78 to −30.67 dB). Fifty of the eyes (35.8%) had undergone glaucoma surgery. Thirty-two of the patients (42.7%) had a family history of glaucoma; the mean interval between the two visits was 18.66 ± 9.55 days (range, 5–38 days).

Test–Retest Variability

Test–retest variability and the 95% limits of agreement for the number of test locations falling beyond the 5% level of normality for mfVEP and SITA tests are given in Figures 1 and 2. These figures show a significant amount of test–retest variability for both tests with the limits of agreement being slightly larger for the mfVEP test than SITA perimetry (13.39 and 9.88, respectively). This difference reversed when higher cut-off levels (2% and 1%) were used (Table 1). Prior experience with threshold perimetry, but not mfVEP, might have influenced the measured variability with the two tests.

The inclusion criteria of visual field loss (Glaucoma Hemifield Test outside normal limits) on the first visit, accounts for the absence of patients with zero defective locations on visit 1, but not on visit 2. This may have introduced a small bias in the data.

Quadrant and Hemifield Spatial Agreement

The spatial agreement between SITA and mfVEP data was investigated with two by two contingency tables (Table 2), for both the four quadrants and the two hemifields. The cut-off criteria for the defective classification was ≥3 and ≥5 test locations beyond the 5% level of normality for quadrants and hemifield, respectively. These values were chosen to give specificities of less than, but close to 2%. For comparison purposes, similar contingency tables were compiled for visits 1 and 2 of both tests with the limits of agreement being beyond the 95% level of normality than SITA (mean difference 4.64 ± 14.62, Fig. 5), although the difference was small and reduced further at higher cut-off levels (98% level, mean 2.93 ± 12.03).

These differences between the two tests were often large and difficult to explain on the basis of test–retest variability. To investigate this point further, the differences were compared between visits 1 and 2. Figure 6 shows that the differences between the two tests are consistent and are not, therefore, due to test–retest variability.

To investigate whether this finding was related to the amplitude of the mfVEP signals, the differences between SITA perimetry and mfVEP were compared to the summed amplitude of the mfVEP data (Fig. 7). This figure shows a strong relationship (P < 0.0001) between these two measures, as the summed amplitude of the mfVEP signal reduces the mfVEP results show more defective test locations than the visual field test.

Reliability Indices and Test Times

The reliability indices for SITA perimetry showed no statistically significant relationship to test–retest variability, (FL: P = 0.289; FP: P = 0.052; FN: P = 0.300). A poor relationship was also found between the mfVEP test and its reliability indices (FL: P = 0.349; FP: P = 0.698).

The mean time (± SD) taken to perform mfVEP on both eyes was 33.60 ± 3.02 minutes while SITA perimetry took approximately 20 minutes (~8 minutes per eye in cases of visual field loss with 4 minutes setup/change over time). Despite the time difference and the fact that the mfVEP test is more invasive, 73 of the 74 patients preferred the mfVEP test. The main stated reasons were that the test was easier and less stressful. Many individuals found conventional perimetry boring and confusing. Physical comfort was also a factor for many patients.
DISCUSSION

Our test–retest measures of SITA perimetry show a large degree of variability, a finding which is in agreement with previous studies.\textsuperscript{15,21–23} This large degree of variability in patients with prior experience of threshold perimetry limits the capacity of current perimetric techniques to quantify change and provide accurate predictions of long-term outcomes. This shortcoming of current perimetric techniques has encouraged the development of alternate technologies such as the mfVEP. This study found that the test–retest variability of mfVEP was slightly larger than SITA perimetry in a sample of patients with glaucomatous visual field loss and no prior experience of mfVEP. The current mfVEP technique does not, therefore, seem to offer any advantages over current perimetric techniques when it come to quantifying change and predicting long term outcomes.

Goldberg et al.\textsuperscript{16} examined the coefficient of variation for the amplitude of the mfVEP in normal subjects, and the same research group investigated the coefficient of variation in glaucoma suspects and confirmed cases of glaucoma (Graham SL, et al. \textit{IOVS} 2003;44:ARVO E-Abstract 45). The glaucoma patients demonstrated significantly more variability than the normal subjects and suspect glaucoma patients. The variability was higher in areas of smaller signal amplitude and the authors concluded that a large change in the amplitude is needed to confirm progression of a visual field defect. Furthermore, they
suggested improved signal-to-noise ratio should improve reproducibility.

The spatial agreement between mfVEP and SITA perimetry was similar to that recently reported by Hood et al. Agreement was generally in the region of 70%–75%, but when corrected for chance using the kappa statistic was found to be only “fair to moderate.” For comparison the agreement between repeat measures with the same test (mfVEP and SITA perimetry) was found by the kappa statistic to be “good”.

An unexpected finding of this study was the occasional large disparity between the number of test locations falling beyond the 95% level of normality with the two tests. This disparity was not consistently in one direction. In some patients the mfVEP marked more locations as being abnormal than SITA perimetry, whereas with other patients it was the other way around. Similar findings have been reported by other researchers. Further investigation of these disparities between mfVEP and SITA perimetry revealed that they were consistent from one session to another (i.e., if a patient had more defective locations with mfVEP at visit 1, then a similar result would be obtained at visit 2). This finding indicated that the differences between the two tests could not be explained on the basis of random variability. Further analysis of the differences between the two tests revealed a relationship with the amplitude (peak-to-trough) of the VEP signal. In cases where the amplitude was low, the mfVEP tended to classify more test locations as being abnormal than did SITA perimetry. When the VEP amplitude was high, the mfVEP test classified fewer locations as being abnormal.

The signal-to-noise ratio of mfVEP varies from subject to subject and has been highlighted by other research groups as an important parameter of test performance. Changes in electrode resistance and cortical architecture are two of the parameters that influence this ratio. To compensate for differences in the signal-to-noise ratio, the mfVEP signal undergoes a certain amount of processing. This processing should be independent of defect size. The results of the present study indicate that this is not the case and that a negative relationship exists between signal amplitude and the number of locations classified as outside normal limits.

Visual field reliability estimates have previously been shown to have low reliability. The poor relationship between visual field reliability indices and test-retest variability found in this study is not, therefore, surprising. It does, however, highlight the inadequacy of reliability indices at providing the clinician with useful information regarding test-retest variabil-
ity. The mfVEP reliability estimates FL and FP are derived from the patients’ responses to the fixation target. Patients are instructed at the onset of the test to press a response button every time a number 3 appears at the fixation point. If the patient fails to press the response button when a number 3 is presented, this is recorded as a FL. If the patient presses the button when a different number is displayed, this is recorded as a FP. While both FPs and FLs were found to increase with the number of defective test locations, there was little relationship between these measures of reliability and test–retest performance. This again signifies that these measures of reliability have little clinical value. The use of an infrared video camera that monitors the patient’s eye movements could give valuable information about fixation accuracy. None of the patients were unable to perform the visual field test, although this might simply reflect the fact that one of the inclusion criteria was prior experience with the HFA. Two patients had to be excluded from the study because the mfVEP responses were very noisy. One patient was constantly head-shaking and the other patient was having difficulty maintaining fixation due to a visual acuity of +0.5 LogMAR. Recently, it was highlighted that cataract, uncorrected refractive error, and unsteady fixation can produce apparent mfVEP defects (Winn BJ, et al. IOVS 2003;44:ARVO E-Abstract 32).

Multifocal VEP is a relatively new technology compared with perimeter and as such is still evolving at a fairly rapid rate. It should be possible to modify the mfVEP software to remove the relationship between the number of locations classed as defective and the signal amplitude or, at least, to highlight when the signal amplitude is likely to lead to erroneous results. Test–retest variability needs to be improved if mfVEP is going to provide a more reliable measure of change and a better predictor of long term outcomes than STA perimeter.

References