Short Duration Transient Visual Evoked Potentials in Glaucomatous Eyes

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Purpose: To investigate the correlation between structural and functional damage in patients with asymmetric glaucoma using a newly developed short duration transient visual evoked potential (SD-tVEP) device.

Methods: Twenty-five patients with visual acuity $\geq 20/30$ and asymmetric visual field (VF) loss [inter-eye difference in mean deviation index (MD) of at least 3 dB] were enrolled. Patients underwent optical coherence tomography (OCT) for macular thickness measurement, scanning laser polarimetry with variable corneal compensation for retinal nerve fiber layer measurement, and SD-tVEP (10% and 85% Michelson contrast, acquisition time of 20 s) in both eyes within 2 months. We correlated VF MD and structural test results with SD-tVEP P100 latency and Delta Amplitude (N75-P100).

Results: Using 10% contrast, there was a significant difference in SD-tVEP latency and amplitude between eyes with better and worse VF MD ($P < 0.001$). MD correlated significantly with both SD-tVEP parameters ($r > 0.33$, $P \leq 0.01$). When using 85% contrast, SD-tVEP amplitude differed between eyes ($P = 0.01$) and MD values correlated significantly with amplitude results ($r = 0.32$, $P = 0.01$), but not with latency ($P = 0.46$). In eyes with more advanced VF loss, there was a positive and significant correlation between SD-tVEP amplitude (85% contrast) and macular thickness on OCT ($r = 0.47$, $P = 0.01$), but not with retinal nerve fiber layer measured with polarimetry ($P = 0.26$).

Conclusions: In cases of asymmetric glaucoma, SD-tVEP results correlate significantly with the level of VF damage as measured by MD. In the eyes with more advanced VF loss, reduced SD-tVEP amplitude was associated with decreased macular thickness on OCT. These findings suggest that SD-tVEP may be a fast and objective method to assess or screen for functional damage in glaucomatous eyes.

Key Words: glaucoma, visual evoked potential, optical coherence tomography, scanning laser polarimetry

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Despite recent technologic advances, glaucoma diagnosis and management is still based primarily on clinical assessment of the visual field (VF) and the optic nerve. To improve detection of early damage and its progression over time, numerous studies have analyzed structure-function correlations in glaucomatous eyes.[1–5] Although different technologies for objective and quantitative measurement of structural damage have emerged, glaucomatous functional damage is typically evaluated by subjective, psychophysical testing using standard achromatic automated perimetry (SAP).[1,3–8,9]

The conventional pattern, reversal visual evoked potential (VEP) technique,[10] is an objective method of evaluating the integrity of the visual pathway. Electrodes placed in standardized positions detect electrical signals generated by the visual cortex while the patient fixates at the center of a reversing checkerboard pattern stimulus. Although the conventional pattern—reversal VEP—could be potentially useful for the detection of visual abnormalities, problems such as positioning of electrodes, limited repeatability, subjective analysis of the waveforms, and long-test duration have mitigated against its use in clinical practice.[10]

Improvements on the original technique that could eliminate some or all of these problems have the potential to increase the clinical applicability of VEP screening for a range of diseases that affect the visual pathway. The Diopsys Enfant short duration transient VEP (SD-tVEP) system (Diopsys, Inc, Pine Brook, NJ) decreases test duration substantially by means of synchronized signal acquisition in combination with a postprocessing technique that provides less subjectivity in waveform assessment.[11] Recently, investigating the repeatability of SD-tVEP in normal subjects, we found good within-session, inter-session repeatability, and good inter-eye correlation and agreement.[12] In addition, it has shown promise as a screening tool for detecting visual deficits in young children, and seems to have overcome some of the obstacles faced by the standard VEP technique.[11] In this study, we investigated the correlation between structural and functional damage in patients with asymmetric glaucoma using the SD-tVEP technique.

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MATERIALS AND METHODS

This prospective study was carried out at the New York Eye and Ear Infirmary. The study was approved by the institutional review board and followed the tenets of the Declaration of Helsinki. Written informed consent was obtained from all patients.

Patients

Twenty-five patients with glaucomatous optic neuropathy and characteristic VF defects (Humphrey Field Analyzer II, SITA-Standard program 24-2, Carl Zeiss Meditec, Inc, Dublin, CA) confirmed on 2 separate examinations were prospectively enrolled. All patients underwent a complete ophthalmologic examination and had clear media, best corrected visual acuity $\geq 20/30$, equal pupils greater than 3 mm, and asymmetric VF loss defined as an inter-eye difference in MD of at least 3 dB. Subjects with ocular diseases other than glaucoma such as diabetes or neurologic disease were excluded.

Glaucomatous optic neuropathy was defined as asymmetry of the cup-to-disc ratio ≥ 0.2 between eyes, presence of generalized or localized retinal nerve fiber layer (RNFL) defects, or neuroretinal rim defects in the absence of any other abnormalities that could explain such findings. A glaucomatous VF was defined as a glaucoma hemifield test outside normal limits on at least 2 consecutive baseline VF tests and the presence of at least 3 contiguous test points within the same hemifield on the pattern standard deviation plot at P value less than 1%, with at least 1 at P value less than 0.5%, excluding points on the edge of the field or those directly above and below the blind spot.

Tests and Data Collection

Data collected included patient demographics, clinical findings, and diagnostic testing results. Both eyes of each patient were included in the analysis and were separated into 2 groups based upon mean deviation (MD). All patients underwent optical coherence tomography (Stratus OCT-3, Carl Zeiss Meditec, Inc, Dublin, CA) for macular thickness measurement, scanning laser polarimetry with variable corneal compensation (GDx-VCC, Carl Zeiss Meditec, Inc, Dublin, CA) for peripapillary RNFL measurement, and SD-tVEP (10% and 85% Michelson contrast, acquisition time of 20 s) in both eyes, all tests being performed within 2 months from each other.

Optical Coherence Tomography (Stratus OCT)

Macular thickness measurements were carried out using the fast macular thickness map protocol (scan length, 6.0 mm). All patients were dilated before the examination. To be included in the analysis, scans needed to have a signal strength ≥ 7, be well focused on the fundus, and centered on the fovea. Three concentric circles divide the macular thickness map into 3 zones: fovea, inner macula, and outer macula (total of 9 regions). To avoid multiple correlations, only the average of the 4 inner macula thickness measurements (3 mm radius from the center of the fovea) was used in the structure and functional correlation analysis.

Scanning Laser Polarimetry With Variable Corneal Compensation (GDx-VCC)

Details of this technique have been described earlier.[5] To be included in the analysis, scans needed to be well-focused, evenly illuminated, and well centered. Images with atypical patterns of retardation were not included, as they can have unreliable RNFL thickness measurements. We used only 1 GDx-VCC parameter, the temporal-superior-nasal-inferior-temporal (TSNIT) average (global peripapillary RNFL thickness measurement), in the structure and functional correlation analysis.

SD-tVEP Test

SD-tVEP were generated using a modified Diopsys Enfant System. The stimulus was presented on a γ-corrected Phillips 170B7 17-inch LCD monitor, running at 75 frames/s. Luminance output over time was verified using a luminance meter MavoSpot 2 USB (Gossen, GmbH, Nuremberg, Germany). Gold cup electrodes (10 mm) and commercially available skin preparation and EEG paste were used for recording of the SD-tVEP. Synchronized single-channel SD-tVEPs were recorded, generating a time series of 240 data points per analysis window. The room luminance was maintained at scotopic conditions (< 0.3 NITS). Preadaptation was unnecessary for the SD-tVEP recordings.[10] Artifact rejection was used during SD-tVEP data recording. Each phase reversal was monitored for blinking and eye movement. If a phase reversal was rejected, an additional phase reversal was added to the run. If 50% of the phase reversals were rejected, then the entire run was rejected. Thus, the maximum run time was limited to 30 seconds. Each phase reversal is 500 ms and 40 phase reversals are required for a successful run.

Stimulus

In all cases, the display was viewed through natural pupils with optimal refractive correction in place. The viewing distance was set to 1 m, yielding a total display viewing angle of 12.6 degrees. The circular black/white checkerboard pattern reversal stimulus had a diameter of 22 cm with a red circular ring used as a fixation target. The diameter of this target was 1 cm with a ring thickness of 1 mm. The target ring was centered on the stimulus. The check size was 28.9 minutes of arc. Two pattern contrasts were used in the study, based on earlier studies that suggested that differential contrast stimulation could affect the VEP waveforms.[13,14] The first pattern had white checks of 122.9 cd/m^2 and black checks of 101.1 cd/m^2 resulting in a Michelson contrast of 10% and mean luminance of 112.0 cd/m^2. The second pattern had white checks of 122.9 cd/m^2 and black checks of 9.6 cd/m^2 resulting in a Michelson contrast of 85% and mean luminance of 66.3 cd/m^2. The 2 patterns are referred to as 10% contrast and 85% contrast in this study.

During a recording session, the contrast polarity of each stimulus check was temporally modulated at a reversal frequency of 1 Hz (2 pattern reversals equates to 1 reversal cycle); therefore, each reversal occurred at 2 Hz or twice per second. This stimulus is termed a pattern reversal stimulus and has a duty cycle of 50%.[10] The 10% and 85% contrast stimuli were presented for each eye (the fellow eye was covered) for 20 seconds, unless artifacts were detected in which additional pattern reversals were added with a maximum time of 30 seconds. Any test that lasted longer than 30 seconds was rejected. Each eye was tested twice. The right eye was arbitrarily chosen as the first one to be tested for all patients. A 3-minute rest period was provided between runs. The first 2 tests were first performed at 10% contrast and then repeated at the 85% contrast level.

Recording Procedures

One EEG channel was recorded using gold cup electrodes. The electrodes were placed 4 cm above the inion (active) and on the frontal tuberosity, a feature of the frontal bone that forms the "bumps" in the forehead, centered on the midline (reference). Although this deviates from the International Society for Clinical Electrophysiology of Vision protocol of 10% of the inion-nasion distance, an approximation of 4 cm was used to decrease overall test preparation time. The left side of the forehead just in front of the temple served as ground.

In preparation for recording, the skin at each electrode site was scrubbed with Nuprep (D.O. Weaver & Co, Aurora, CO) on a cotton-tipped wooden swab. Electrodes were fixed in position with Ten20 conductive paste (D.O. Weaver & Co, Aurora, CO) and secured with a small gauze pad with conductive paste applied. Electrode impedance was maintained below 10 kΩ in all cases and was usually below 5 kΩ.

The gain of the EEG analog amplifier/filter module (Diopsys Enfant Amp 100, Diopsys, Inc, Pine Brook, NJ) was 10,000 and the band-pass of the filtered was 0.5 to 100 Hz. The EEG signal was sampled at 600 Hz using the Enfant System's A/D converter. As a note, the 10,000 gain was the only gain in the entire data acquisition path, including the A/D Analog to Digital (A/D) convertor. The A/D convertor offers a series of bipolar voltage ranges (± 1.25, ± 2.50, ± 5.0, and ± 10.0 V). These ranges are used to increase or decrease resolution of the sampled signal. There is no gain multiplier. Therefore, for the 4 ranges of resolutions for the A/D would be 610 μV/quantum, 1.22, 2.44, and 4.88 mV/quantum, respectively. Reflecting these resolutions to preamplification, the resolutions would be 61, 122, 244, and 488 nV/quantum, respectively. For this study, the A/D convertor had a resolution of 12 bits, resulting in 4096 quanta. The voltage range of the A/D was programmed to (−) 1.25 V to (+) 1.25 V, therefore having a resolution of 610 μV/quantum.

Data Analysis

The stored SD-tVEP data for each subject was exported from the device's relational database to an external binary file to be processed by an external signal processing algorithm.[15] The data had the N75-P100-N135 complex temporal epoch identified by windowing and bilateral band pass filtering using Derr's extraction method.[6] The low pass cut-off frequency was chosen to be 30 Hz. The high pass frequency was set to 5.1 Hz so as to minimize low frequency drift. Reducing this drift enhances an automated method for isolating the N75-P100-N135 complex. The automated method is based on a mathematical model of the tVEP in which the parameters are optimized to reduce the least square error between the model and the SD-tVEP response. By eliminating the direct current drift, the number of model parameters can be reduced thus increasing accuracy and reducing computational time.[16] P100 amplitude and P100 latency were identified from the filtered N75-P100-N135 complex.

We used paired *t* test to compare SD-tVEP parameters between the group of eyes with better MD and the group of fellow eyes with worse MD. The correlation between VF MD index and SD-tVEP Delta P100-N75 amplitude and P100 latency was assessed using linear regression analysis. The same analysis was performed replacing VF MD values for the average of the central 12 and central 4 points of the total deviation plot. In addition, we evaluated the correlation between SD-tVEP parameters and structural test results (OCT, macular thickness; GDx-VCC, peripapillary RNFL thickness) separately in eyes with better and worse MD. A final subanalysis was performed to assess the ability of each SD-tVEP parameter to discriminate between healthy and glaucomatous eyes (a total of 20 healthy subjects from our normative database were included). One eye per patient was selected randomly for analysis. Receiver operating characteristic (ROC) curves and sensitivities at fixed specificities were generated for the following SD-tVEP parameters: SD-tVEP amplitude—10% of contrast, SD-tVEP amplitude—85% of contrast, SD-tVEP latency—10% of contrast, and SD-tVEP latency—85% of contrast.

RESULTS

Mean patient age was 61.5 ± 16 years. Most patients were women (76%), White (60%), and had open-angle glaucoma (72%). Demographic and clinical data for all patients are summarized in Table 1. There was a significant difference in MD values between the more and less affected eyes (-13.7 ± 6.7 dB vs. -3.8 ± 1.9 dB, $P < 0.001$; paired *t* test) and both RNFL and macular thickness were significantly less in the more affected eyes ($P < 0.01$; Table 2).

Referencing Table 2's SD-tVEP 10% contrast data, there was a significant difference in SD-tVEP latency and amplitude between eyes with better and worse VF MD ($P < 0.001$ for both measurements). When using 85% contrast data, only SD-tVEP amplitude had a significant difference between eyes ($P = 0.01$).

Regarding the correlations between VF and SD-tVEP results, VF MD correlated significantly with both SD-tVEP parameters at 10% contrast ($r > 0.33$, $P \leq 0.01$). When using 85% contrast, VF MD values correlated significantly with amplitude results ($r = 0.32$, $P = 0.01$), but not with latency ($P = 0.46$). Considering only the average of the central 12 and central 4 points of the total deviation plot (instead of using MD values), stronger correlations were found between VF and SD-tVEP results. At 10% contrast, both SD-tVEP parameters correlated significantly with the average values of the central 12 ($r > 0.40$, $P < 0.01$) and central 4 ($r > 0.42$, $P < 0.01$) VF points. At 85% contrast, although significant correlations were found between SD-tVEP amplitude and the average values of the central 12 ($r = 0.36$, $P < 0.01$) and 4 ($r = 0.39$, $P < 0.01$) VF points, no significant correlations were found for SD-tVEP latency.

TABLE 1. Demographic and Clinical Characteristics

Variable	Patients (n = 25)
Age (y)	61.5 ± 16.1
Sex (male/female)	6/19
Race (W/AD/H/A)	15/3/4/3
Mean baseline BCVA (logMAR)	0.11 ± 0.1
Glaucoma diagnoses (%)	
Primary open-angle glaucoma	40 (10/25)
Chronic angle-closure glaucoma	28 (7/25)
Others	32 (8/25)

Data are given as mean ± SD whenever indicated.

A indicates Asian; AD, African descent; BCVA, best corrected visual acuity; H, Hispanic; logMAR, logarithmic minimal angle resolution; W, White.

TABLE 2. Results From Functional and Structural Tests

Parameters	Eyes With Better MD	Fellow Eyes With Worse MD	P*
SD-tVEP 10% contrast latency (ms)	111.6 ± 13.1	150.5 ± 38.1	< 0.001
SD-tVEP 10% contrast amplitude (mV)	4.2 ± 2.4	2.3 ± 1.1	< 0.001
SD-tVEP 85% contrast latency (ms)	109.4 ± 10.2	110.5 ± 13.3	0.75
SD-tVEP 85% contrast amplitude (mV)	8.3 ± 5.4	6.4 ± 3.6	0.01
Average RNFL thickness (GDx-VCC, μm)	46.4 ± 8.4	38.3 ± 8.5	< 0.01
Macular thickness (Stratus OCT, μm)	258.2 ± 20.9	240.3 ± 30.1	< 0.01

Data are given as mean ± SD.
*Comparison between the group of eyes with better MD and the group of fellow eyes with worse MD using paired *t* test.
GDx-VCC indicates scanning laser polarimetry with variable corneal compensation; MD, visual field mean deviation index; OCT, optical coherence tomography; RNFL, retinal nerve fiber layer; SD-tVEP, short duration transient visual evoked potential.

Table 3 indicates that in eyes with more advanced VF loss, there was a positive and significant correlation between SD-tVEP amplitude (85% contrast) and macular thickness on OCT ($r = 0.47$, $P = 0.01$), but not with GDx-VCC TSNIT average ($r = 0.24$, $P = 0.26$). No significant structure-function correlation was observed when using 10% contrast or during assessment of less affected eyes.

We did an additional subanalysis to evaluate the structure-function relationship in eyes with central VF defects (1 point with $P \leq 1\%$ within the 4 central points of the 24-2 VF test). Using 85% contrast, the correlation between macular thickness on OCT and SD-tVEP amplitude increased ($r = 0.67$; $P < 0.01$), whereas the correlation between the same SD-tVEP parameter and the RNFL thickness (GDx-VCC TSNIT average) remained nonsignificant ($P = 0.54$). All the other correlations remained nonsignificant.

Finally, regarding the diagnostic ability of each SD-tVEP parameter to discriminate between healthy and glaucomatous eyes [similar mean age between glaucomatous (61.5 ± 16 y) and nonglaucomatous patients (56.5 ± 11.3 y; $P > 0.05$)], we found that areas under the ROC curves for SD-tVEP amplitude—10% and 85% were 0.82 and 0.71, respectively. For SD-tVEP latency—10% and 85%, areas under the ROC curves were 0.58 and 0.61, respectively. Areas under the ROC curves for SD-tVEP amplitude were significantly larger than those for latency ($P < 0.05$). Although SD-tVEP amplitude—85% had the highest sensitivity at 80% specificity (70.4%, cut-off 3.15 mV), SD-tVEP latency—85% had the lowest sensitivity at 80% specificity (33.8%, cut-off 113.3 ms). When only patients with early glaucoma (MD up to −6 dB) were considered, amplitude—10% (area under curve, 0.75) had the best diagnostic performance.

DISCUSSION

We correlated a new, rapid, and objective electrophysiologic test (SD-tVEP) with the results of a well-established functional test (SAP) and 2 tests of structural damage in glaucomatous eyes with asymmetric functional damage based on SAP results. To the best of our knowledge, this is the first study to evaluate the SD-tVEP technique in eyes with glaucoma.

We found a significant correlation between SAP and SD-tVEP in glaucomatous eyes. Eyes with worse MD had a more delayed latency and reduced amplitude. This is consistent with earlier studies using conventional VEP techniques.[17–20] Although amplitude correlated with MD values at both 10% and 85% contrast, latency correlated significantly with MD at 10% contrast, but not at 85%, suggesting a better performance of this technique at lower contrast stimulus. As expected, when the most central points of the total deviation plot were considered (instead of VF MD values), stronger correlations were found between SAP and SD-tVEP results. Even though the VF MD index takes into account the eccentricity of each point (is weighted down for peripheral points), it is reasonable that the use of the average values of the central VF points would provide stronger correlations, as the VEP stimulus only covered the most central area of the VF. There is little agreement regarding glaucomatous damage and latency delay.[17,18,21] Parisi et al,[17] evaluating the same VEP parameters used in this study (at 80% contrast), found both latency and amplitude to be abnormal in patients with open-angle glaucoma compared with controls. In addition, both VEP parameters correlated significantly with the severity of the VF damage (MD). Towle et al[18] also found abnormally long VEP latencies in eyes with glaucomatous

TABLE 3. Correlation Between Short Duration Transient Visual Evoked Potential Results and Structural Tests

	Eyes With Better MD		Fellow Eyes With Worse MD	
Parameters	r	P*	r	P*
10% contrast latency versus macular thickness	0.33	0.15	0.20	0.41
10% contrast latency versus RNFL thickness	0.14	0.58	0.33	0.14
10% contrast amplitude versus macular thickness	0.31	0.14	0.34	0.10
10% contrast amplitude versus RNFL thickness	0.18	0.55	0.27	0.21
85% contrast latency versus macular thickness	0.04	0.74	0.24	0.31
85% contrast latency versus RNFL thickness	0.10	0.65	0.14	0.50
85% contrast amplitude versus macular thickness	0.12	0.56	0.47	0.01
85% contrast amplitude versus RNFL thickness	0.10	0.64	0.24	0.26

*Linear regression analysis.
MD indicates visual field mean deviation index; RNFL, retinal nerve fiber layer.

VF defects and a similar correlation between SAP and VEP results using an 84% contrast stimulus. In contrast, Grippo et al[21] did not observe any significant relationship between latency (at 100% contrast) and VF damage in glaucomatous eyes using multifocal VEP (mfVEP) technique. They also found that less than 15% of glaucomatous eyes had latencies outside the range of control eyes. We believe further investigation is necessary to elucidate the relationship between latency delay and the SD-tVEP technique.

There is scant information regarding structure-function correlation in glaucoma using conventional VEP techniques. Parisi et al[22] observed no significant correlation between RNFL thickness and conventional VEP changes with a wide range of VF loss (MD, −5 to −28 dB). They did not evaluate macular thickness. Most similar reports used a mfVEP technique instead of conventional VEP.[23–25] For instance, Kanadani et al[23] observed good agreement between functional defects and macular thickness in glaucoma using OCT. Balachandran et al[24] found limited correlation between confocal scanning laser ophthalmoscopy and mfVEP results.

Using a new VEP technique, which increases signal-to-noise ratio providing less subjectivity in waveform assessment, we found that decreased SD-tVEP amplitude correlated significantly with reduced macular thickness in the eyes with more advanced damage. Although this correlation increased when considering only the eyes with central VF defects, the correlation between the same SD-tVEP parameter and peripapillary RNFL measurements remained nonsignificant. This could possibly be explained by the fact that VEP evaluation is focused in the central 20 degrees of the VF, and central VF loss assessed by both SAP and VEP techniques correlates well with macular thickness values using OCT.[23] In addition, the lack of correlation with GDx-VCC measurements is not surprising given that this device is designed to assess peripapillary RNFL thickness rather than macular pathology. Although the GDx-VCC is widely used to assess peripapillary RNFL thickness, it would have been interesting if the OCT was used to obtain both macular and RNFL thickness measurements. It is worth noting that the macular nerve fibers measured with OCT do not match exactly with the population of photoreceptors and retinal ganglion cells stimulated during SAP or SD-tVEP testing. Rather, these are passing fibers from other retinal areas, including the macula. Even though it has been suggested that macular ganglion cells loss is masked in perimetry by redundancy and receptive field overlap in central vision,[26] a better structure-function relationship could have been observed if the macular ganglion cell layer was measured rather than the RNFL. Finally, the fact that a poor correlation was found in eyes with less advanced VF damage is in agreement with other studies that found better correlation between structural and functional tests in eyes with more advanced disease.[3,6]

We found weak or no correlations between SD-tVEP results and structural measurements. Considering that VEP responses depend on the magnitude and timing of afferent inputs to the visual cortex and result from both retinal activity and neural conduction along the postretinal visual pathways, additional postretinal factors could then contribute to the observed reduced amplitude and delayed latency that we found in these patients.[27] Earlier studies have suggested that the impaired VEP responses observed in glaucomatous optic neuropathy could be attributed not only to impaired neural conduction in the optic nerve, but to the entire postretinal visual pathway.[28–30] Using 1.5-Tesla magnetic resonance imaging, Gupta et al[31] recently demonstrated significant atrophy of the lateral geniculate nucleus in patients with glaucoma and vision loss compared with normal subjects.

In summary, using a SD-tVEP technique, we found good correlation between VEP results (especially amplitude) and the level of VF damage in patients with asymmetric glaucoma. Moreover, eyes with decreased VEP amplitude also had reduced macular thickness. Although these structural and functional correlations require confirmation in a larger glaucoma population with different disease stages, they suggest that SD-tVEP warrants further investigation as a fast and objective method to assess functional damage in glaucomatous eyes.

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