Visual Function Correlates with Nerve Fiber Layer Thickness in Eyes Affected by Ocular Hypertension

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Purpose. To test whether the high variability observed when measuring pattern electroretinogram (PERG), visual evoked potentials (VEP), and spatial contrast sensitivity (SCS) in eyes with ocular hypertension is associated with variation in nerve fiber layer thickness, as measured by optical coherence tomography (OCT).

Methods. The study involved 32 untreated eyes (32 patients; age range, 29–64 years) showing a normal white-on-white 24/2 Humphrey (San Leandro, CA) perimetry, IOP between 23 and 28 mm Hg, best corrected acuity of 20/20 or better, and none of the following papillary signs on conventional color stereo slides: rim notch(es), peripapillary splinter hemorrhages, or increased vertical-to-horizontal cup-to-disc ratio. On recruitment, each eye underwent SCS testing, OCT, PERG, and VEP recordings. Linear regression (Pearson's test) or Spearman's rank regression was adopted for the analysis of the data.

Results. The 95% confidence limits of the electrophysiological data were: PERG P50 latency, 59.3 to 63 msec; PERG P50 to N95 amplitude, 0.74 to 1.15 μmV; VEP P100 latency, 113 to 118 msec; VEP N75 to P100 amplitude, 3.81 to 4.90 μmV. The 360° nerve fiber layer thickness overall (NFLO) ranged between 113 and 169 μm (145 ± 16 μm; mean ± SD) and significantly correlated with PERG P50 to N95 amplitude (r: 0.518; $P = 0.002$), PERG P50 latency (r: −0.470; $P = 0.007$), VEP N75 to P100 amplitude (r: 0.460; $P = 0.008$), VEP P100 latency (r = −0.422; $P = 0.016$) and SCS at 3 cyc/deg (r: −0.358; $P = 0.044$).

Conclusions. The variability of PERG, VEP, and SCS testing observed in eyes with ocular hypertension is associated with differences in NFL thickness (the thinner the layer, the worse the visual function). (*Invest Ophthalmol Vis Sci.* 1999;40:1828–1833)

Psychophysical[1] and electrophysiological[2,3] experiments have described impaired visual function in human eyes having high intraocular pressure (IOP) but showing a normal visual field tested by white-on-white computer-assisted static perimetry. However, a significant overlap exists between normal subjects and those with ocular hypertension.[2,3]

Optical coherence tomography (OCT), a recently developed technique, allows in vivo scanning of the retinal layers. The device is based on the interferometry principle, with a superluminescent diode used as a source. The resolution limits are approximately 10 μm.[4] Measurements of retinal thickness are obtained automatically by means of a computer algorithm that searches for the characteristic changes in reflectivity observed at the superficial and deep retinal boundaries.[4] Experiments performed on glaucomatous eyes have extensively shown topographical correlation between visual field defects and localized or diffused thinning of the nerve fiber layers (NFLs).[5]

We applied OCT to eyes with ocular hypertension and no visual field defects. The data on the NFLs were then correlated with both electrophysiological (pattern electroretinogram [PERG] and visual evoked potentials [VEPs]) and psychophysical (spatial contrast sensitivity [SCS]) parameters. Thus, we tested whether the reported variability is associated with interindividual variation in NFL thickness.

Methods

Thirty-two eyes of 32 consecutive patients (age range, 29–64 years, mean, 48 ± 9 years) affected by ocular hypertension were recruited. Each patient had to be experienced with automatic perimetry (at least six reliable examinations within the previous 3 years). Enrollment was conducted according to the following inclusion criteria: IOP more than 23 mm Hg and less than 28 mm Hg (average of the two highest readings of the daily curve, from 8:00 AM to 6:00 PM, six independent readings, one every 2 hours); normal automatic full threshold perimetry (24/2 Humphrey, mean defect, corrected pattern standard deviation and glaucoma hemifield test within the normal range of the database of the Humphrey [San Leandro, CA]) software; fixation losses, false-positive rate and false-negative

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rate each <20%); best corrected visual acuity 20/20 or better; none of the following papillary signs on conventional color stereo slides: rim notch(es), peripapillary splinter hemorrhages, increased vertical-to-horizontal cup-to-disc ratio, cup-to-disc asymmetry between the two eyes less than 0.2; mean refractive error (when present) between −0.50 and +0.50 spherical equivalent; no previous history of diabetes, optic neuritis, or any disease involving the anterior visual pathways; and pupil diameter 3 mm or more.

On recruitment, each patient provided informed consent to the procedures. The research followed the tenents of the Declaration of Helsinki.

Each eye underwent the following procedures: SCS testing and OCT were performed on the same day; PERG and VEP recordings were performed 1 week later.

OCT Examination

OCT (Humphrey) was performed using a fiber-optic delivery system coupled with slit lamp biomicroscope. This system provides the operator with a video camera view of the scanning probe beam on the fundus and an OCT image acquired in real time on a computer monitor.

After dilation with 1% tropicamide, each eye was scanned three times using a 3.4-mm circle (1.7-mm radius). Near-infrared light (840-nm wavelength) was used. Throughout scanning, the patient kept the eyes fixed on an internal target provided by the equipment. The measurements were obtained from three nonconsecutive scans (i.e., the patient was allowed to rest for a few seconds before repositioning to proceed to the next scan).

The OCT software has an automated computer algorithm that identifies the anterior and posterior border of the retina, making it possible to calculate NFL and total retinal thickness overall by quadrant and by clock hour.

In the assessed eyes, we considered the average of the values obtained by three different measurements in each quadrant: superior (NFLS), inferior (NFLI), nasal (NFLN), and temporal (NFLT); the overall data obtained in all quadrants (12 values averaged) were identified as NFL overall (NFLO).

Contrast Sensitivity Examination

Foveal SCS was tested by using a commercial available chart (CSV1000 (Vector Vision, Daytona, OH). The CSV1000 provides a fluorescent luminance source that retroilluminates a translucent chart. The instrument houses a series of photocells that automatically monitor and calibrate the instrument light level to 85 candelas (cd)/m^2 ± 0.1 log unit. At the testing distance of 8 feet, the translucent chart presents four spatial frequencies, each on a separate row of the test: 3, 6, 12, and 18 cyc/deg. Sensitivity levels at each frequency range from 0.7 to 2.08 (3 cyc/deg), 0.91 to 2.29 (6 cyc/deg), 0.61 to 1.99 (12 cyc/deg), and 0.17 to 1.55 (18 cyc/deg) log units.

The procedure described by Pomerance and Evans[1] was followed. Sensitivity threshold was measured two times, allowing only a few seconds between measurements. Only the second measurements were considered for analysis. The test–retest variability was consistent with that reported previously[1].

Electrophysiological Examination

Simultaneous recordings of transient VEPs and PERGs were assessed using a method previously published.[3] The subjects under examination were seated in a semidark, acoustically isolated room in front of a display that was surrounded by a uniform field of luminance of 5 cd/m^2. The subjects were informed of the type of examination and its diagnostic uses. Before the experiment, each subject was adapted to the ambient room light for 10 minutes, and the pupil diameter was approximately 5 mm. Miotic or mydriatic drugs were not used.

The visual stimuli were checkerboard patterns (contrast 70%, mean luminance 110 cd/m^2) generated on a TV monitor and reversed in contrast at the rate of two reversals per second. At the viewing distance of 114 cm the check edges subtended 15 minutes of visual angle and the screen of the monitor subtended 12.5°. The refraction of all subjects was corrected for the viewing distance. We used 15 minutes of visual angle, because this smaller size is considered optimal to stimulate the fovea in pattern electroretinography as well.[3] The stimulation was monocular, with occlusion of the contralateral eye.

PERG Recordings

This bioelectrical signal was recorded by a small Ag/AgCl skin electrode placed over the lower eyelid. PERGs were derived bipolarly between the stimulated eye (active electrode) and the patched eye (reference electrode). The ground electrode was in Fpz. The interelectrode resistance was lower than 3 kΩ.

The signal was amplified (gain 50,000), filtered (band-pass, 1–30Hz), and averaged with automatic rejection of artifacts (200 events free from artifacts were averaged for every trial) by BM 6000 (Biomedica Mangoni, Pisa, Italy). The analysis time was 250 msec.

The transient PERG response is characterized by a series of waves with three subsequent peaks, of negative, then positive, then negative polarity. In normal subjects when the conditions of our experiment are used, these peaks have the following mean latencies: 35, 50, and 95 msec.

VEP Recordings

Cup-shaped Ag/AgCl electrodes were fixed with collodion in the following positions: active electrode at Oz, reference electrode at Fpz, ground on the left arm. The interelectrode resistance was kept below 3 kΩ. The bioelectric signal was amplified (gain 20,000), filtered (band-pass, 1–100 Hz), and averaged (200 events free from artifacts were averaged for every trial) by BM 6000. The analysis time was 250 msec.

The transient VEP response is characterized by a series of waves with three sequential peaks, of negative, then positive, then negative polarity. In normal subjects and in the conditions of our experiment, these peaks have the following mean latencies: 75, 100, and 145 msec.

In the recording session, simultaneous PERGs and VEPs were recorded with at least two replications, and the resultant waveforms were superimposed to check the repeatability of the results. We accepted PERG and VEP signals with signals-to-noise ratio more than 2. The noise was measured by recording the bioelectrical signals (200 averaged events) while the monitor was screened by a cardboard and a noise less than 0.1 μV (mean 0.085 μV) was observed in all subjects tested.

For all PERGs and VEPs the peak latency and the peak amplitude of each of the averaged waves were measured directly on the displayed records by means of a pair of cursors. By comparing the VEP peak latency (P100) and the PERG peak latency (P50), it is possible to have an index of postretinal

TABLE 1. Observed Characteristics in Patients with Ocular Hypertension

	Age (y)	IOP*	NFLO†	NFLS	NFLI	NFLN	NFLT	P50‡	P50–N95§	P100‖	N75–P100¶	RCT#	SCS 3 cyc/deg	SCS 6 cyc/deg	SCS 12 cyc/deg	SCS 18 cyc/deg
RG	58	26	113	120	142	123	66	70	0.5	124	2.0	54	1.64	1.85	1.40	0.96
PS	56	25	123	127	149	112	104	63	0.7	112	4.0	49	1.49	1.38	1.25	0.64
PC	58	24	125	136	142	111	107	63	0.5	117	5.7	54	1.49	1.55	1.40	1.11
CA	48	26	129	157	135	123	102	68	0.7	121	4.8	53	1.49	1.85	1.55	1.11
PA	56	25	135	139	154	157	91	62	0.4	116	6.9	54	1.49	1.55	1.40	1.11
CR	61	23	136	133	145	130	136	64	0.7	120	2.6	56	1.17	1.38	1.08	0.64
PD	49	24	143	166	162	135	111	66	1.0	120	5.3	54	1.49	1.85	1.40	1.26
CB	48	26	143	139	151	148	124	67	0.7	124	2.9	57	1.49	1.85	1.55	1.11
CL	47	24	147	158	178	135	117	68	1.2	125	2.3	57	1.49	1.85	1.40	0.96
PB	49	26	151	167	162	160	115	60	0.8	120	3.8	60	1.49	1.85	1.40	1.26
LT	52	22	160	170	176	152	142	61	0.8	125	2.6	64	1.49	1.38	1.08	0.64
CI	64	24	152	170	170	148	121	66	1.1	115	5.4	49	1.49	1.70	1.25	0.96
SB	58	25	163	168	170	165	161	59	1.1	116	5.2	57	1.17	1.38	0.91	0.81
PR	56	26	167	174	176	161	157	62	1.0	113	5.6	51	1.34	1.85	1.55	0.64
CB	38	24	165	176	179	140	166	60	1.3	112	5.5	52	1.34	1.70	1.85	1.11
TR	52	24	128	136	146	114	116	68	0.6	125	2.4	57	1.49	1.70	1.25	0.81
VS	35	25	160	143	189	161	149	57	0.8	118	4.8	61	1.34	1.85	1.55	1.11
FD	35	23	127	141	142	106	122	68	0.5	119	2.2	51	1.34	1.85	0.91	0.81
SC	58	23	169	178	184	163	142	61	1.2	116	6.2	55	1.17	1.38	1.08	0.81
BT	45	23	159	186	159	137	155	52	1.8	102	6.2	50	1.64	1.85	1.55	1.11
LB	45	25	127	143	140	118	108	52	1.6	117	3.6	65	1.64	1.70	1.40	0.96
PD	48	26	151	163	165	146	148	58	1.2	103	7.2	45	1.49	1.55	1.25	0.64
GI	49	24	140	147	158	136	119	54	1.2	115	3.8	61	1.49	1.85	1.55	1.11
TI	49	25	158	154	167	155	157	63	1.0	114	3.9	51	1.34	1.70	1.40	0.64
RE	29	26	131	129	133	133	129	59	1.1	113	4.0	54	1.79	2.00	1.70	1.41
EF	30	24	156	178	175	157	115	55	0.9	111	4.1	56	1.49	2.00	1.70	1.41
OL	42	24	136	157	167	128	89	58	1.2	110	5.2	52	1.49	1.85	1.70	0.96
VO	44	26	154	187	173	127	129	56	1.2	113	4.0	57	1.34	1.70	1.55	0.64
SP	48	22	165	188	193	122	157	55	1.4	103	7.2	48	1.49	1.85	1.40	0.81
BE	39	23	120	132	142	110	93	66	0.5	125	2.3	59	1.64	1.85	1.55	1.26
ED	41	26	167	196	187	148	135	57	1.0	114	4.0	57	1.49	1.85	1.55	1.11
CS	60	25	147	149	153	133	133	60	0.7	114	3.9	54	1.17	1.55	1.25	0.64

* Average of the two highest IOP values in the daily curve in millimeters of mercury.
† All NFL data are in micrometers.
‡ PERG P50 peak latency in milliseconds.
§ PERG P50 to N95 amplitude in microvolts.
‖ VEP P100 peak latency in milliseconds.
¶ VEP N75 to P100 amplitude in microvolts.
# Difference between VEP P100 and PERG P50 latencies in milliseconds.

neural conduction. We call the difference between VEP P100 latency and PERG P50 latency retinocortical time (RCT).[3]

Statistics

Spearman rank and linear regression analysis (Pearson's test) were adopted to evaluate the correlations among SCS, PERG, and VEP parameters and the NFL thickness determined by OCT. Data are expressed as mean ± SD.

RESULTS

The data collected from each patient are displayed in Table 1. The electrophysiological recordings produced the following results (95% confidence limits): PERG P50 latency, 59.3 to 63 msec; PERG P50 to N95 amplitude, 0.74 to 1.15 μmV; VEP P100 latency, 113 to 118 msec; VEP N75 to P 100 amplitude, 3.81 to 4.90 μmV.

The variability of the electrophysiological data were examined as a function of NFL thickness. As shown in Figure 1A, 1B, 1C, and 1D, the experimental points can be fit by linear regressions whose level of significance is reported in Table 2A.

The thickness of the NFL, measured across the 360° section along the optic disc (NFLO), ranged between 113 and 169 μm (145 ± 16 μm). The NFLO values of each patient showed a significant correlation with PERG P50 to N95 amplitude (r: 0.518; $P = 0.002$), PERG P50 latency (r: −0.470; $P = 0.007$), VEP N75 to P 100 amplitude (r: 0.460; $P = 0.008$), and VEP P100 latency (r: −0.422; $P = 0.016$). Because the software of the OCT allows the dissection of four quadrants from the 360° scan, we tested each sector for possible correlation with the electrophysiological data. As shown in Table 2A, PERG and VEP parameters correlated well with the NFL data obtained by OCT in the NFLS, NFLT, NFLI, and temporal (NFLT, including the papillomacular bundle) sector.

NFLO was correlated with SCS threshold measured at 3 cyc/deg (r: −0.358; $P = 0.044$); NLFI and NFLT were also significantly ($P < 0.01$) correlated with SCS threshold measured at 3 cyc/deg. No apparent correlation was observed between SCS measured at 6, 12, and 18 cyc/deg and the OCT data. The levels of significance for each correlation are detailed in Table 2B. Age and IOP showed no correlation with OCT-measured NFL thickness (see Table 2A for details).

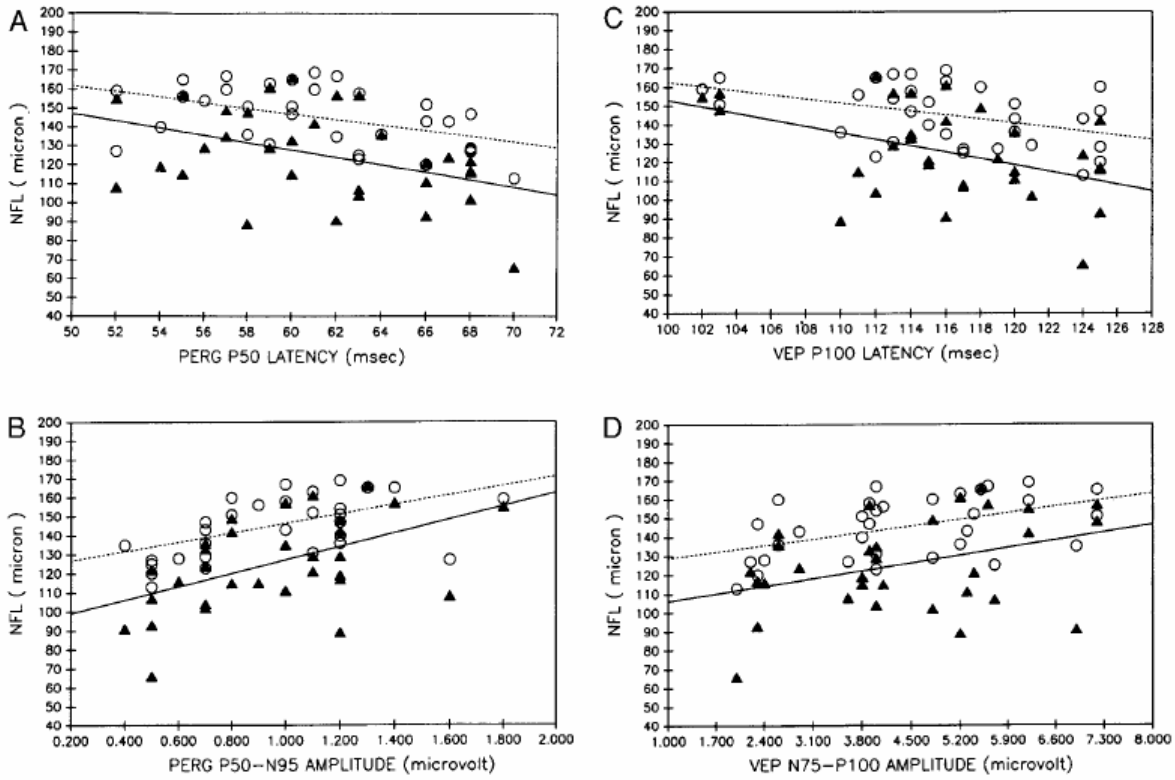

FIGURE 1. NFLO (○, *dashed line*) and NFLT (▲, *solid line*) plotted versus PERG P50 latency (**A**), PERG P50 to N95 amplitude (**B**), VEP P100 latency (**C**), and VEP N75 to P100 amplitude (**D**). Statistical analysis is reported in Table 2A.

DISCUSSION

In this study, we examined eyes with ocular hypertension and no evidence of field damage, and we measured NFL thickness (OCT), PERGs, VEPs, and SCS.

When considering eyes affected by high IOP and no sign of field damage, the actual risk for a conversion to glaucoma is not presently known. Because our study was carried out cross-sectionally, no information is available to determine which eye would eventually have a field defect.

The NFL thickness range obtained by OCT analysis in our study eyes is consistent with that previously reported in a similar population.[6] Most of the eyes showed OCT values well above the suggested lower limits for normal subjects (125–135 μm).[5] The scattering of the electrophysiological data (see. Fig. 1) is consistent with that previously observed by investigators in several studies of ocular hypertension.[2,3] When plotting the data as a function of the OCT values, data can be fit by linear regression. A similar phenomenon is observed for the 3-cyc/deg threshold of SCS. These correlations, albeit moderate (see Table 2), show a strong significance. This result suggests that eyes having a thinner ganglion cell layer, produce smaller electrophysiological (both retinal [PERG]) and cortical [VEP]) and psychophysical responses.

Several psychophysical studies have found that contrast sensitivity to low spatial frequency patterns is impaired in patients affected by glaucoma[7] and that the difference between glaucoma and other diseases, leading to a pathologic contrast sensitivity, appears to be in the low-frequency region[8]. As pointed out by Bodis-Wollner, [8] low spatial frequency refers to patterns with a frequency near, but lower than, the peak of the human foveal contrast sensitivity curve. Three cycles per degree fits this model. Should a lower signal from the OCT (i.e., a thinner NFL) represent a sign of early ganglion cell loss,[7] 3 cyc/deg would be the most likely affected frequency among those tested by the CSV1000 chart. Not surprisingly, then, 3 cyc/deg was the only frequency with a threshold that correlated well with the NFL thickness in our series of hypertensive eyes (see Table 2B).

Studies performed in animal models have shown that the PERG reflects the bioelectrical activity of the innermost retinal layers (the ganglion cells and their fibers).[9] The existence of similar evidence in humans is still controversial.[10] However, if the PERG generators in humans are in the innermost retinal layers, then our data show an intriguing relationship between an electrophysiological bioelectrical response (PERG) and its supposed anatomic counterpart (i.e., the innermost retina) in humans.

Age may have been a potentially confounding factor in the analysis of the data. However, as shown in Table 2A, there was no correlation between age and NFL thickness measured in our cohort of patients. Therefore, we believe that this potential source of bias was, in our study, negligible.

TABLE 2. Linear Regression (A) and Rank Regression (B) between NFL Thickness and Electrophysiological or SCS Parameters

(A)	Age	IOP	PERG P50 Latency	PERG P50–N95 Amplitude	VEP P100 Latency	VEP N75–P100 Amplitude	RCT (P100–P50)
NFLO	*r*: −0.034	*r*: −0.096	*r*: −0.470	*r*: 0.518	*r*: −0.422	*r*: 0.460	*r*: −0.071
	t: −0.187	*t*: −0.527	*t*: −2.916	*t*: 3.318	*t*: −2.546	*t*: 2.835	*t*: −0.389
	P = 0.853	*P* = 0.602	*P* = 0.007	*P* = 0.002	*P* = 0.016	*P* = 0.008	*P* = 0.700
NFLS	*r*: −0.102	*r*: −0.130	*r*: −0.476	*r*: 0.606	*r*: −0.485	*r*: 0.474	*r*: −0.140
	t: −1.565	*t*: −0.716	*t*: −2.968	*t*: 4.168	*t*: −3.035	*t*: 2.949	*t*: −0.775
	P = 0.575	*P* = 0.480	*P* = 0.006	*P* <0.000	*P* = 0.005	*P* = 0.006	*P* = 0.443
NFLI	*r*: 0.065	*r*: −0.190	*r*: −0.378	*r*: 0.422	*r*: −0.334	*r*: 0.391	*r*: −0.041
	t: 0.361	*t*: −1.059	*t*: −2.238	*t*: 2.549	*t*: −1.951	*t*: 2.328	*t*: −0.225
	P = 0.720	*P* = 0.298	*P* = 0.033	*P* = 0.015	*P* = 0.060	*P* = 0.026	*P* = 0.816
NFLN	*r*: 0.086	*r*: 0.216	*r*: −0.253	*r*: 0.181	*r*: −0.126	*r*: 0.344	*r*: 0.107
	t: 0.475	*t*: 1.216	*t*: −1.435	*t*: 1.009	*t*: −0.695	*t*: 2.005	*t*: 0.587
	P = 0.637	*P* = 0.233	*P* = 0.162	*P* = 0.321	*P* = 0.493	*P* = 0.054	*P* = 0.561
NFLT	*r*: −0.061	*r*: −0.151	*r*: −0.404	*r*: 0.493	*r*: −0.447	*r*: 0.349	*r*: −0.168
	t: −0.335	*t*: −0.839	*t*: −2.420	*t*: 3.102	*t*: −2.738	*t*: 2.109	*t*: −0.935
	P = 0.740	*P* = 0.408	*P* = 0.022	*P* = 0.004	*P* = 0.010	*P* = 0.043	*P* = 0.357

(B)	SCS 3 cyc/deg	SCS 6 cyc/deg	SCS 12 cyc/deg	SCS 18 cyc/deg
NFLO	*r*: −0.359	*r*: 0.004	*r*: 0.098	*r*: −0.138
	P = 0.044	*P* = 0.980	*P* = 0.590	*P* = 0.448
NFLS	*r*: −0.225	*r*: 0.081	*r*: 0.132	*r*: −0.054
	P = 0.216	*P* = 0.661	*P* = 0.471	*P* = 0.767
NFLI	*r*: −0.371	*r*: 0.050	*r*: 0.085	*r*: −0.160
	P = 0.037	*P* = 0.784	*P* = 0.645	*P* = 0.383
NFLN	*r*: −0.343	*r*: 0.096	*r*: 0.012	*r*: −0.042
	P = 0.054	*P* = 0.602	*P* = 0.946	*P* = 0.822
NFLT	*r*: −0.412	*r*: −0.093	*r*: −0.073	*r*: −0.340
	P = 0.020	*P* = 0.611	*P* = 0.688	*P* = 0.057

We also observed a strong correlation between VEP electrophysiology and OCT. The cortical evoked response (VEP) is derived from retinal activity together with neural conduction along the visual pathways.[3] When simultaneously recording PERG and VEP, an index of neural conduction (the so-called RCT) can be obtained.[3] In patients with glaucoma, a delay in postretinal visual pathways (i.e., increased RCT) has only been observed once an eye has an actual field defect.[3] Eyes with ocular hypertension, but without field defects, have shown normal postretinal neural conduction.[3] Comparable data may be obtained from the recordings obtained in our cohort of patients. As shown in Table 1, RCT calculated in our study (54.8 ± 4.55 msec) can be superimposed on that previously reported in a cohort of patients with ocular hypertension (54.3 ± 4.12 msec)[3]. We can, therefore, assume that the postretinal neural conduction in our cohort of patients was within the normal range. Therefore, the variability of the VEP response, observed in our patients, would be best explained by differences in the retinal anatomy only. The correlation between NFL thickness and the VEP responses (see Table 2A) suggests that, in our cohort of ocular hypertensive eyes, the neural conduction in the visual pathways was dominated by the retinal component (i.e., the thinner the layers, the worse the conduction).

In conclusion, the data collected in our study show that the variability of the PERG, VEP and SCS threshold observed in eyes with ocular hypertension, is correlated with interindividual variation in NFL thickness (the thinner the layer, the worse the visual function). In human eyes, the NFL thickness measured by OCT is correlated with electrophysiological responses assumed to be originating in the innermost retinal layers.

However, we want to emphasize that a significant correlation between two factors does not imply causality. Other as yet unrecognized factors may contribute to the observed variability of functional parameters in eyes with ocular hypertension.

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