Effects of Coenzyme Q10 in Conjunction With Vitamin E on Retinal-evoked and Cortical-evoked Responses in Patients With Open-angle Glaucoma

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Purpose: To evaluate pattern-evoked retinal and cortical responses [pattern electroretinogram (PERG) and visual-evoked potential (VEP), respectively] after treatment with coenzyme Q10 in conjunction with vitamin E in open-angle glaucoma (OAG) patients.

Methods: Forty-three OAG patients (mean age, 52.5 ± 5.29 y; intraocular pressure < 18 mm Hg with β-blocker monoterapy only) were enrolled. At baseline and after 6 and 12 months, simultaneous recordings of PERG and VEPs were obtained from 22 OAG patients who underwent treatment consisting of coenzyme Q10 and vitamin E (Coqun, 2 drops/d) in addition to β-blocker monoterapy (GC group), and from 21 OAG patients who were only treated with β-blockers (GP group).

Results: At baseline, intraocular pressure, PERG, and VEP parameters were similar in both GC and GP groups (analysis of variance, $P > 0.05$). After 6 and 12 months, PERG and VEP response parameters of GP patients were unchanged when compared to baseline. In GC patients, PERG P50 and VEP P100 implicit times were decreased, whereas PERG P50-N95 and VEP N75-P100 amplitudes were increased ($P < 0.01$) when compared to baseline. In the GC group, the differences in implicit times and amplitudes with respect to baseline were significantly larger ($P < 0.01$) than those recorded in the GP group. The improvement (12 mo minus baseline) of VEP implicit time was significantly correlated with the changes of PERG P50-N95 amplitude ($r = -0.66171$, $P = 0.0008$) and P50 implicit time ($r = 0.68364$, $P = 0.00045$) over a period of 12 months.

Conclusions: Coenzyme Q10 associated with vitamin E administration in OAG shows a beneficial effect on the inner retinal function (PERG improvement) with consequent enhancement of the visual cortical responses (VEP improvement).

Key Words: glaucoma, PERG, VEP, coenzyme Q10

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In patients affected by open-angle glaucoma (OAG), electrophysiological recordings may provide selective information about dysfunction occurring in the retinal preganglionic elements [abnormal flash electroretinogram (ERG)],[1] in ganglion cells and their fibers [impaired pattern electroretinogram (ERG)],[2–6] or in the whole visual pathway [abnormal visual-evoked potentials (VEPs)].[7–11]

In the management of OAG, the possibility of influencing the progression of visual dysfunction has constituted a constant effort for years. Toward this end, and by using an electrophysiological approach, it was observed that different treatments may improve the retinal function and the neural conduction along the visual pathways. In fact, an improvement of PERG responses (ranging from 10% to 200%[12,13]) may be obtained after lowering the intraocular pressure (IOP) with β-blockers[14–16] or acetazolamide,[17] and after treatment with nicergoline,[18] citicoline,[19–21] and epigallocatechin-gallate.[22] In addition, it was observed that nicergoline[18] and citicoline[19–21] also enhance VEP responses.

Several studies have suggested the hypothesis that the oxidative stress may play a causative role in the glaucomatous ganglion cells dysfunction and consequently in their loss (see Tezel,[23] for a review). Thus, compounds with antioxidant properties may be candidate treatments in order to prevent the ganglion cell impairment. On the basis of the experimental evidence,[24,25] coenzyme Q10[26] is a molecule with antioxidant properties that may have a potential protective effect on the glaucomatous ganglion cell dysfunction. This may constitute a rationale for the use of coenzyme Q10 in OAG patients. Unfortunately, topical treatment using solely coenzyme Q10 is not currently available, but can only be found in conjunction with vitamin E [Coqun, Visufarma, Italy, coenzyme Q10 100 mg; d-α tocopheryl polyethylene glycol 1000 succinate (Vitamin E TPGS) 500 mg; plus physiological solution at 100 mL].

Therefore, the aim of our study is to evaluate, using electrophysiological methods (VEP and PERG recordings), whether the treatment consisting of coenzyme Q10 in association with vitamin E, could have any effect on the retinal function, on visual cortical responses, and on neural conduction along the postretinal visual pathways in patients with OAG.

MATERIALS AND METHODS

Patients

Forty-three eyes from 43 patients (range, 42 to 60 y; mean age, 52.5 ± 5.29 y) affected by OAG were recruited.
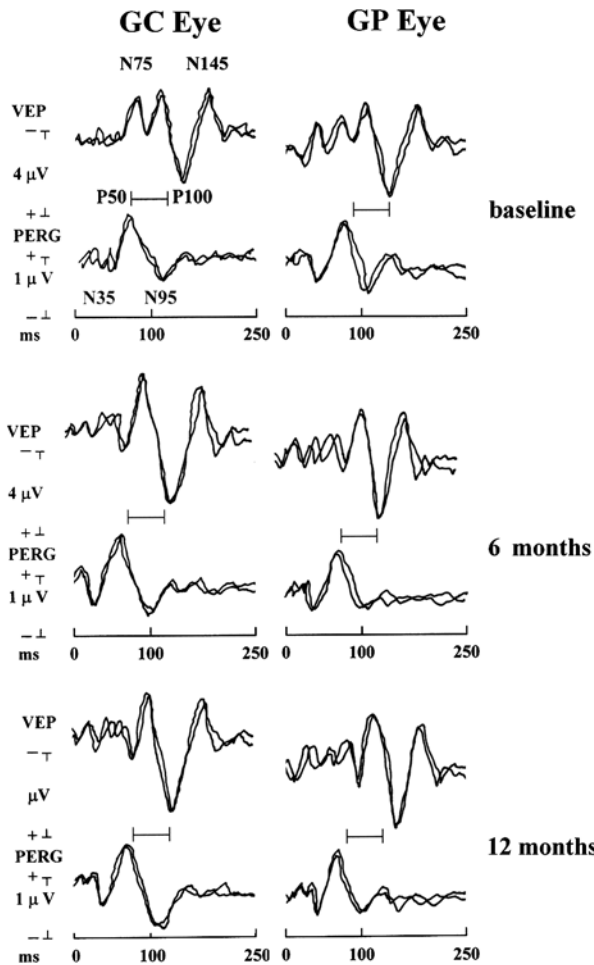
FIGURE 1. Examples of simultaneous visual-evoked potential (VEP) and pattern electroretinogram (PERG) recordings performed in 1 open-angle glaucoma (OAG) patient treated with β-blocker monotherapy with additional Coqun treatment (GC eye) and in 1 OAG patient exclusively treated with β-blocker monotherapy (GP eye). Electrophysiological examinations were assessed in baseline condition and after 6 and 12 months. In comparison with the baseline condition, PERG and VEP recorded in the GC eye showed a decrease in implicit times and an increase in amplitudes, whereas PERG and VEP recorded in the GP eye showed similar implicit times and amplitudes. |———|: Retinocortical Time, difference between VEP P100 and PERG P50 implicit times.

OAG patients were selected from a larger population of 194 OAG patients on the basis of the following inclusion criteria.

- IOP > 23 mm Hg and < 28 mm Hg (average of the 2 highest readings of the daily curve, from 8:00 AM to 6:00 PM, 6 independent readings, 1 every 2 h) without medical treatment.
- Humphrey Field Analysis 24/2 MD > −8 dB; corrected pattern SD (CPSD) < +6 dB; fixation losses, false-positive rate, and false-negative rate each < 20%.
- Best corrected visual acuity ranged from 0.0 to 0.1 logMAR.
- One or more papillary signs on conventional color stereoslides: the presence of a localized loss of neuroretinal rim (notch), thinning of the neuroretinal rim, generalized loss of optic rim tissue, optic disc excavation, vertical or horizontal cup/disc ratio > 0.5, cup-disc asymmetry between the 2 eyes > 0.2, peripapillary splinter hemorrhages.
- Refractive error (when present) between −3.00 and +3.00 spherical equivalent.
- No previous history or presence of any disease involving cornea, lens, macula, or retina.
- No previous history or presence of diabetes, optic neuritis, or any disease involving the visual pathways.
- Pupil diameter > 3 mm without mydriatic or miotic drugs.
- Central corneal thickness assessed by ultrasonic pachymetry performed using AL 2000 Bio & Pachymeter (Tomey Corporation, Japan) within 500 and 600 μm.

Since it is known that PERG responses can be modified by the pharmacological reduction of IOP,[12–17] we only

TABLE 1. Clinical Characteristics Observed in Control Subjects (C eyes) and in Open-angle Glaucoma (OAG) Patients Treated With Coenzyme Q10 Plus Vitamin E (GC Eyes, N = 22) and in Untreated OAG Eyes (GP Eyes, N = 21)

	Mean ± SD	ANOVA Versus Controls	ANOVA Versus GP
Age (y)			
C eyes	51.7 ± 6.04		
GC eyes	52.8 ± 5.46	$F_{1,41} = 0.38;$ $P = 0.539$	$F_{1,42} = 0.18;$ $P = 0.670$
GP eyes	52.1 ± 5.22	$F_{1,40} = 0.05;$ $P = 0.821$	
VA (logMAR)			
C eyes	0.005 ± 0.022		
GC eyes	0.013 ± 0.035	$F_{1,41} = 0.77;$ $P = 0.386$	$F_{1,42} = 0.01;$ $P = 0.926$
GP eyes	0.014 ± 0.035	$F_{1,41} = 0.96;$ $P = 0.333$	
IOP-F			
C eyes	14.4 ± 1.76		
GC eyes	25.0 ± 1.62	$F_{1,41} = 410.4;$ $P < 0.0001$	$F_{1,42} = 0.04;$ $P = 0.834$
GP eyes	24.9 ± 1.49	$F_{1,40} = 422.6;$ $P < 0.0001$	
HFA MD (dB)			
C eyes	−0.63 ± 0.91		
GC eyes	−4.82 ± 1.62	$F_{1,41} = 103.8;$ $P < 0.0001$	$F_{1,42} = 0.07;$ $P = 0.790$
GP eyes	−4.67 ± 2.03	$F_{1,40} = 66.4;$ $P < 0.0001$	
HFA CPSD (dB)			
C eyes	1.28 ± 0.22		
GC eyes	4.04 ± 1.28	$F_{1,41} = 90.3;$ $P < 0.0001$	$F_{1,42} = 0.17;$ $P = 0.683$
GP eyes	3.86 ± 1.58	$F_{1,40} = 52.3;$ $P < 0.0001$	
TE (mo)			
C eyes	—		
GC eyes	18.3 ± 2.74		$F_{1,42} = 0.21;$ $P = 0.651$
GP eyes	17.9 ± 3.02		

ANOVA indicates statistical evaluation by a 1-way analysis of variance; CPSD, corrected pattern SD; HFA, Humphrey 24-2 visual field; IOP-F, intraocular pressure at the time of the first diagnosis of ocular hypertension; SD, 1 mean SD; TE, time elapsed from the diagnosis of increase in IOP; VA, visual acuity.

TABLE 2. Mean Values of the Absolute Values of PERG P50 and VEP P100 Implicit Times, PERG P50-N95 and VEP N75-P100 Amplitudes, of the RCT Detected at Baseline Condition in Control Subjects (C Eyes, N = 20), OAG Patients Treated With Coenzyme Q10 Plus Vitamin E (GC eyes, N = 22), and in Untreated Open-angle Glaucoma Eyes (GP Eyes, N = 21)

	Mean ± SD	ANOVA Versus Controls	No.	Ab
PERG P50 IT (ms)				
C eyes	48.9 ± 1.38			
GC eyes	57.9 ± 4.29	$F_{1,41} = 80.31; P < 0.0001$	1	21
GP eyes	58.2 ± 3.34	$F_{1,40} = 133.2; P < 0.0001$	0	21
PERG P50-N95 A (mV)				
C eyes	3.19 ± 0.312			
GC eyes	1.26 ± 0.468	$F_{1,41} = 242.0; P < 0.0001$	0	22
GP eyes	1.33 ± 0.556	$F_{1,40} = 172.1; P < 0.0001$	0	21
VEP P100 IT (ms)				
C eyes	90.5 ± 2.12			
GC eyes	112.4 ± 5.38	$F_{1,41} = 289.9; P < 0.0001$	0	22
GP eyes	107.1 ± 12.1	$F_{1,40} = 36.5; P < 0.0001$	2	19
VEP N75-P100 A (mV)				
C eyes	18.3 ± 1.64			
GC eyes	6.43 ± 1.74	$F_{1,41} = 514.8; P < 0.0001$	0	22
GP eyes	6.46 ± 4.57	$F_{1,40} = 119.5; P < 0.0001$	1	20
RCT (ms)				
C eyes	41.2 ± 1.26			
GC eyes	54.6 ± 6.19	$F_{1,41} = 75.21; P < 0.0001$	1	21
GP eyes	48.9 ± 12.2	$F_{1,40} = 7.88; P = 0.008$	3	18

Normal limits were obtained from control subjects by calculating mean values + 2SD for PERG and VEP implicit times and RCT and mean values −2 SD for PERG and VEP amplitudes.

A indicates amplitude; Ab, number of eyes outside the normal limits; ANOVA, statistical evaluation by a 1-way analysis of variance versus controls; IT, implicit time; No., number of eyes inside the normal limits; PERG, pattern electroretinogram; RCT, Retinocortical Time; SD, 1 mean SD; VEP, visual-evoked potential.

enrolled OAG patients with IOP values of < 18 mm Hg on β-blocker monotherapy, maintained during the 8 months preceding the first electrophysiological evaluation. IOP was assessed as the average of the 2 highest readings of the daily curve (from 8:00 AM to 6:00 PM, 6 independent readings, 1 every 2 h).

All enrolled patients were randomly (see below) divided into 2 age-similar groups: the first consisted of 22 OAG patients (range, 42 to 60 y; mean age, 52.8 ± 5.46 y) who, in addition to the topical treatment with β-blockers, received a further topical treatment with Coqun (coenzyme Q10 100 mg; vitamin E TPGS 500 mg; physiological solution at 100 mL, Visufarma, Italy, 2 drops/d) for 12 months (22 eyes, Coqun-treated, GC Group); the second was made up of 21 OAG patients (range, 42 to 60 y; mean age, 52.1 ± 5.22 y) who were treated exclusively with β-blocker monotherapy during the same period (21 eyes, Coqun-not treated, GP Group).

Compliance to eye drops application was assessed through a questionnaire, which was distributed by the study personnel during each visit. As expected in a clinical study, reported adherence to treatment was high, and all patients rated their compliance as "good to very good" (regular use of the eye drops in at least 80% of the trial period).

Twenty eyes of 20 normal age-similar subjects (range, 42 to 60 y; mean age, 51.7 ± 6.04 y) provided electrophysiological control data.

Electrophysiological Examinations

In controls, GC and GP eyes, the electrophysiological examination was performed at baseline condition and only in GC and GP eyes after 6 and 12 months of follow-up.

In agreement with previously published studies,[6,7,19,20,21,27,28] simultaneous PERG and VEP recordings were performed using the methods as follows.

Subjects were seated in a semi-dark, acoustically isolated room in front of the display surrounded by a uniformom field of luminance of 5 cd/m². Before the experiment, each subject was adapted to the ambient room light for 10 minutes, with a pupil diameter, measured by a ruler, of approximately 5 mm. Mydriatic or miotic drugs were never used. Stimulation was monocular after occlusion of the other eye. Visual stimuli were checkerboard patterns (contrast 80%, mean luminance 110 cd/m²) generated on a TV monitor and reversed in contrast at the rate of 2 reversals per second. At the viewing distance of 114 cm, the check edges subtended 15 minutes (15′) of visual angle, whereas the monitor screen subtended 18 degrees. PERG and VEP recordings were performed with full correction of refraction at the viewing distance. A small red fixation target, subtending a visual angle of approximately 0.5 degrees (estimated after taking into account spectacle-corrected individual refractive errors) was placed at the center of the pattern stimulus. At every PERG and VEP examination, each patient positively reported that he/she could clearly perceive the fixation target. The refraction of all subjects was corrected for viewing distance.

PERG Recordings

The bioelectrical signal was recorded by a small Ag/AgCl skin electrode placed over the lower eyelid. PERGs were bipolarly derived between the stimulated (active electrode) and the patched (reference electrode) eye using a previously described method.[29] As the recording protocol was extensive, the use of skin electrodes with interocular recording represented a good compromise between the signal-to-noise ratio and signal stability. A discussion on PERGs using skin electrodes and its relationship to the responses obtained by corneal electrodes can be found elsewhere.[30,31] The ground electrode was in Fpz.[32]
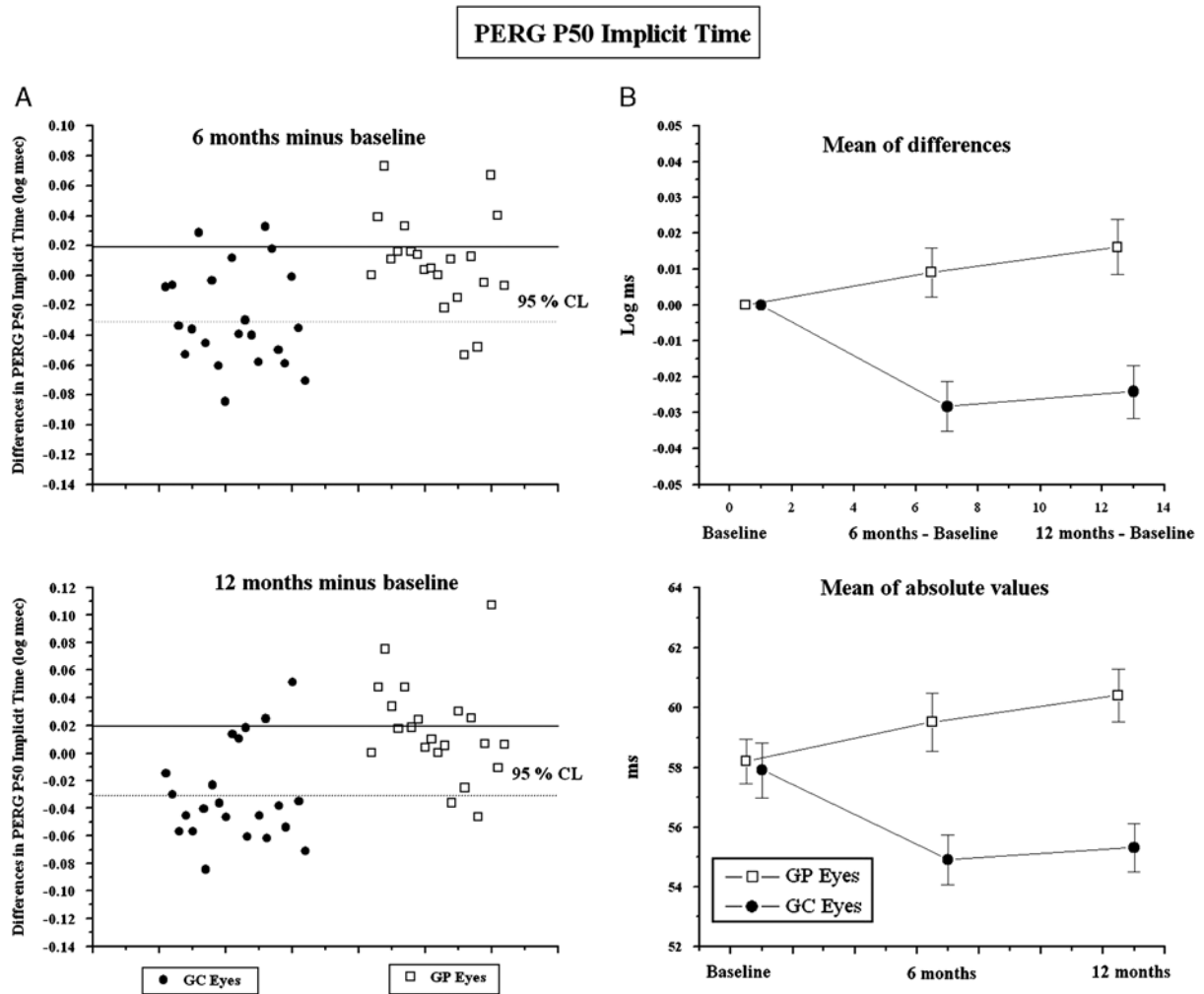
FIGURE 2. Pattern electroretinogram (PERG) P50 implicit time. Individual changes (A) and graphic representation (B) of mean of differences or absolute values observed in open-angle glaucoma (OAG) patients treated with β-blocker monotherapy with additional Coqun treatment (GC eye) and in OAG patient treated exclusively with β-blocker monotherapy (GP eye). The percentage of unmodified eyes (within the 95% confidence test-retest limit), eyes with improvement (values <95% confidence test-retest limit—dashed line) and eyes with worsening (values >95% confidence test-retest limit—solid line) is reported in Table 1. The evaluation of statistical changes is reported for the differences and absolute values in Tables 2 and 3, respectively. Vertical lines—1 SEM.

Interelectrode resistance was < 3000 Ω. The signal was amplified (gain 50,000), filtered (band-pass 1 to 30 Hz) and averaged with an automatic rejection of artifacts (200 events free from artifacts were averaged for every trial) by EREV 2000 (Lace Elettronica, Pisa, Italy). Analysis time was 250 ms.

The transient PERG response is characterized by a number of waves with 3 subsequent peaks of negative, positive, and negative polarity, respectively.

In visually normal subjects, these peaks have the following implicit times: 35, 50, and 95 ms (N35, P50, N95).

VEP Recordings

Cup-shaped electrodes of Ag/AgCl were fixed with collodion in the following positions: active electrode in Oz,[32] reference electrode in Fpz,[32] ground in the left arm. Interelectrode resistance was kept < 3000 Ω. The bioelectric signal was amplified (gain 20,000), filtered (band-pass 1 to 100 Hz) and averaged (200 events free from artifacts were averaged for every trial) by EREV 2000. Analysis time was 250 ms. The transient VEP response is characterized by a number of waves with 3 subsequent peaks of negative, positive, and negative polarity, respectively. In visually normal subjects, these peaks have the following implicit times: 75, 100, and 145 ms (N75, P100, N145).

The simultaneous recordings of PERG and VEP enable the separation of macular from postretinal impairments and provide an "electrophysiological index" of postretinal neural conduction (derived from the difference between VEP P100 and the PERG P50 implicit times), known as "Retinocortical Time (RCT)."[27,33]

During a recording session, simultaneous VEPs and PERGs were recorded at least twice (2 to 6 times) and the resulting waveforms were superimposed to check the repeatability of results. For all PERG and VEPs, implicit times and peak-to-peak amplitudes of each of the averaged
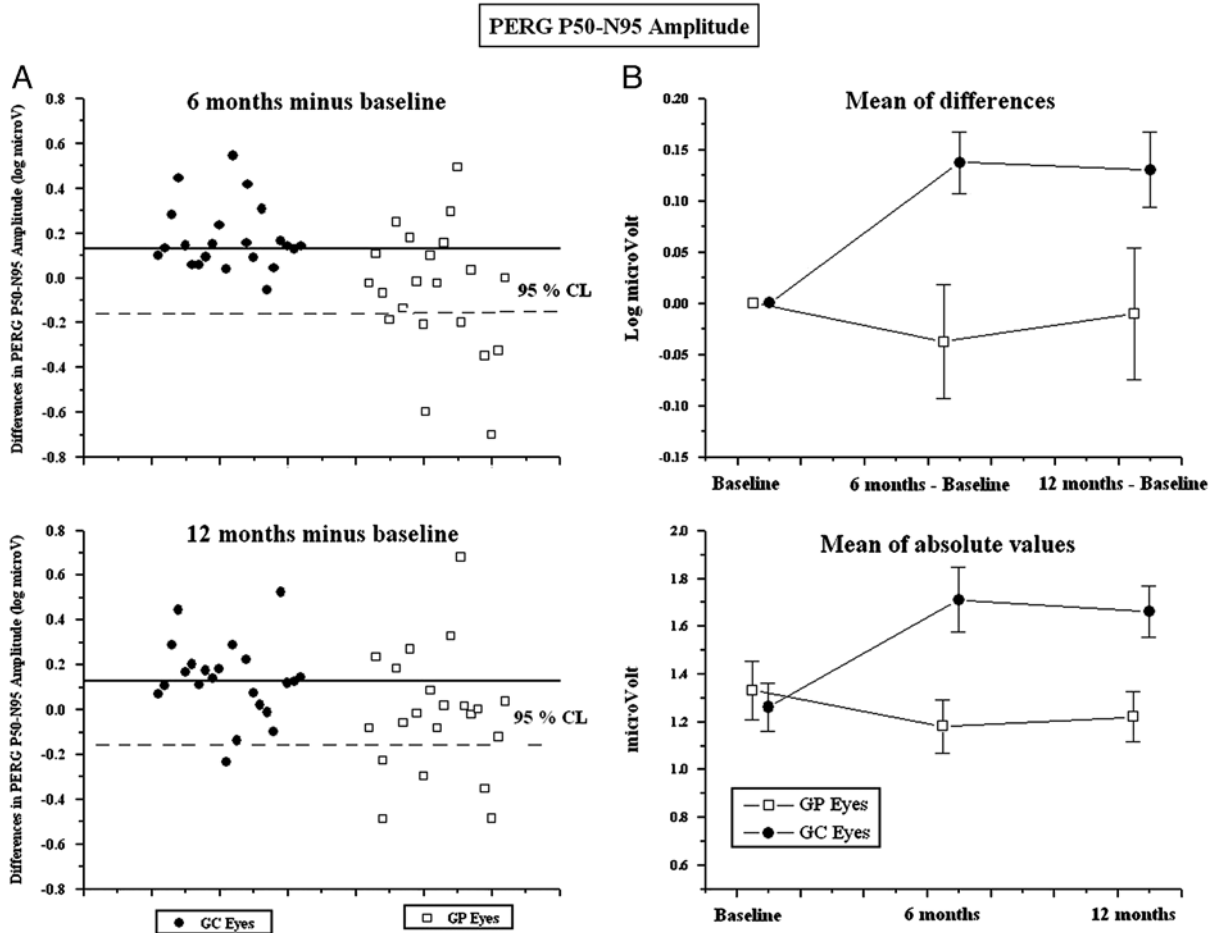
FIGURE 3. Pattern electroretinogram (PERG) P50-N95 amplitude individual changes (A) and graphic representation (B) of mean of differences or absolute values observed in open-angle glaucoma (OAG) patients treated with β-blocker monotherapy with additional Coqun treatment (GC eye) and in OAG patient treated exclusively with β-blocker monotherapy (GP eye). The percentage of unmodified eyes (within the 95% confidence test-retest limit), eyes with improvement (values >95% confidence test-retest limit—solid line), and eyes with worsening (values <95% confidence test-retest limit—dashed line) is reported in Table 1. The evaluation of statistical changes is reported for the differences and absolute values in Tables 2 and 3, respectively. Vertical lines—1 SEM.

waves were directly measured on the displayed records by means of a pair of cursors.

On the basis of previous studies[28] we know that intraindividual variability (evaluated by test-retest) is approximately ±2 ms for PERG P50 and VEP P100 implicit times and approximately ±0.18 mV for PERG P50-N95 and VEP N75-P100 amplitudes. During the recording session, we considered as "superimposable," and therefore repeatable, 2 successive waveforms, with a difference in milliseconds (for PERG P50 and VEP P100 implicit times) and in microvolts (for PERG P50-N95 and VEP N75-P100 amplitudes) that was less than the above-reported values of intraindividual variability. At times, the first 2 recordings were sufficient to obtain repeatable waveforms; however, in other instances, further recordings were required (albeit never more than 6 in the cohort of patients). For statistical analyses (see below), we considered PERG and VEP values measured in the recording with the lowest PERG P50-N95 amplitude.

In each patient, the signal-to-noise ratio (SNR) of PERG and VEP responses was assessed by measuring a "noise" response, whereas the subject fixated an unmodulated field of the same mean luminance as the stimulus. At least 2 "noise" records of 200 events each were obtained, and the resulting grand average was considered for measurement. The peak-to-peak amplitude of this final waveform (ie, the average of at least 2 replications) was measured in a temporal window corresponding to that same amplitude at which the response component of interest (ie, VEP N75-P100, PERG P50-N95) was expected to peak. SNRs for this component were determined by dividing the peak amplitude of the component by the noise in the corresponding temporal window. We observed an electroretinographic noise <0.1 mV (mean 0.079 mV, range 0.065 to 0.090 mV, resulting from the grand average of 400 to 1200 events), and an evoked potential noise <0.16 mV (mean 0.098 mV, range 0.080 to 0.112 mV, resulting from the grand average of 400 to 1200 events) in all subjects that were tested. Moreover, for all subjects and patients, we accepted VEP and PERG signals with a SNR of >2.

Following a criterion previously used in other published works,[34,35] in order to evaluate the PERG and VEP responses independently from the clinical conditions of the
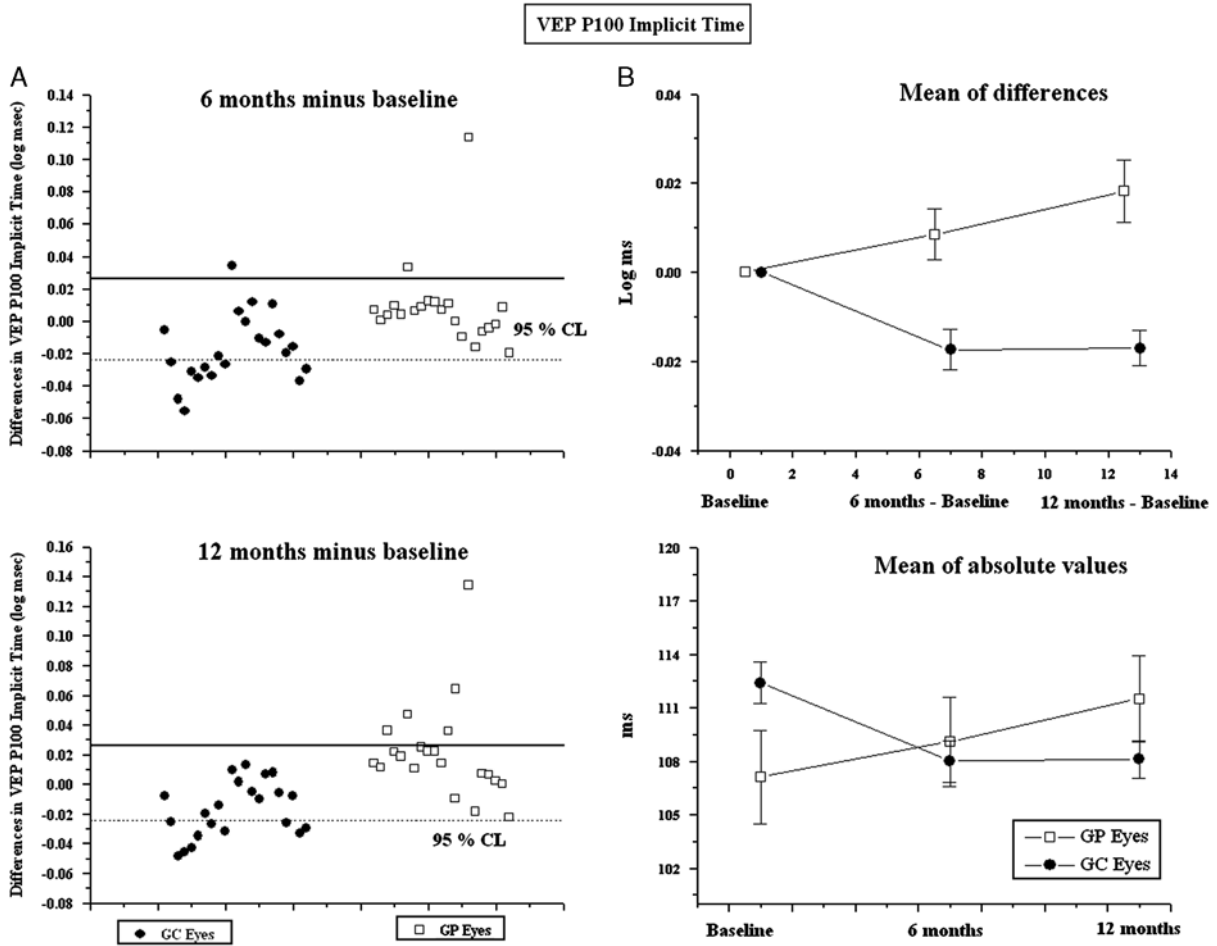
FIGURE 4. Visual-evoked potential (VEP) P100 implicit time. Individual changes (A) and graphic representation (B) of mean of differences or absolute values observed in open-angle glaucoma (OAG) patients treated with β-blocker monotherapy with additional Coqun treatment (GC eye) and in OAG patient treated exclusively with β-blocker monotherapy (GP eye). The percentage of unmodified eyes (within the 95% confidence test-retest limit), eyes with improvement (values <95% confidence test-retest limit—dashed line) and eyes with worsening (values >95% confidence test-retest limit–solid line) is reported in Table 1. The evaluation of statistical changes is reported for the differences and absolute values in Tables 2 and 3, respectively. Vertical lines—1 SEM.

tested subjects, all electrophysiological examinations were performed at baseline conditions in the presence of four operators (V.P., S.T., D.M., and B.F.), who were masked during the treatment group for each patient. The random separation of Coqun-treated and Coqun-not treated patients was performed by 1 operator (L.T.)—who was the only person aware of the key—in accordance with an electronically generated randomization table. Indeed, all electrophysiological recordings were performed for each of the OAG patients during follow-up sessions at 6 and 12 months, by using the identical conditions performed at baseline (ie, uniform field of luminance of 5cd/m², adaptation to the ambient room light for 10 min, pupil diameter of approximately 5 mm), and the operators V.P., S.T., D.M., and B.F., were unable to know whether the tested patient belonged to the Coqun-treated or Coqun-untreated group. The key was only opened at the end of the follow-up period.

The research followed the tenets of the Declaration of Helsinki. The protocol was approved by the local Ethical Committee. Upon recruitment, each patient was aware that he was being enrolled in a study to test a new topical drug and provided an informed consent.

Statistics

Sample size estimates were obtained from pilot evaluations performed in 20 eyes from 20 OAG eyes and 20 eyes from 20 control subjects, other than those included in the current study (unpublished data). Interindividual variability, expressed as data SD, was estimated for PERG P50-N95 amplitude and VEP P100 implicit time measurements. It was found that data SDs were significantly higher for patients when compared to controls (about 35% vs. 15%). Assuming the above, it was also established that, among SD subjects (35% as they were all OAG patients) in the current study, sample sizes of control subjects and patients belonging to the OAG group provided a power of 90%, at an α = 0.05, detecting a difference between groups of ≥ 55% in PERG P50-N95 amplitude and VEP P100 implicit time measurements. These differences were preliminarily observed by comparing OAG and control data.[28] They were also expected to be electrophysiologically
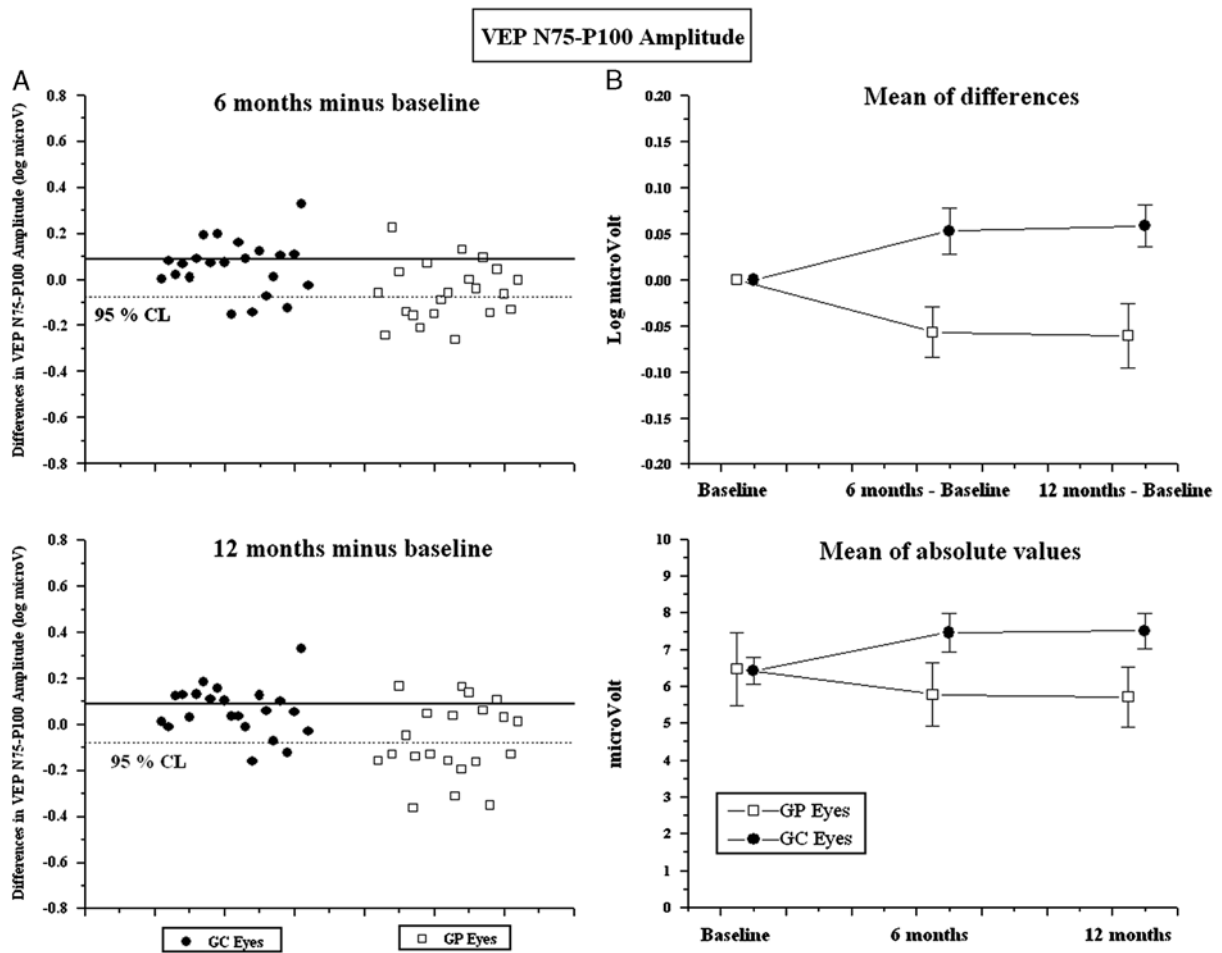
FIGURE 5. Visual-evoked potential (VEP) N75-P100 amplitude. Individual changes (A) and graphic representation (B) of mean of differences or absolute values observed in open-angle glaucoma (OAG) patients treated with β-blocker monotherapy with additional Coqun treatment (GC eye) and in OAG patient treated exclusively with β-blocker monotherapy (GP eye). The percentage of unmodified eyes (within the 95% confidence test-retest limit), eyes with improvement (values >95% confidence test-retest limit—solid line) and eyes with worsening (values <95% confidence test-retest limit—dashed line) is reported in Table 1. The evaluation of statistical changes is reported for the differences and absolute values in Tables 2 and 3, respectively. Vertical lines—1 SEM.

significant when comparing results of treated OAG eyes observed in baseline conditions versus those observed at 6 and 12 months.

Test-retest data (obtained in the group of OAG patients evaluated in this study) of PERG and VEP results were expressed as the mean difference between 2 recordings obtained in separate sessions ± SD of this difference. A 95% confidence limit (CL) (mean ± 2 SD) of test-retest variability in OAG patients was established assuming a normal distribution.

The differences of PERG and VEP response values between groups (GC eyes vs. GP eyes) were evaluated by a 1-way analysis of variance. Changes in the PERG and VEP responses that were observed in GC eyes and GP eyes when compared to baseline were evaluated by analysis of variance for repeated-measures. After the different treatments, the differences that were observed in individual OAG eyes with respect to the baseline values, were calculated performing a logarithmic transformation to better approximate normal distribution.

Pearson correlation was used to correlate the changes during the follow-up of all electrophysiological parameters (PERG, VEP, and RCT values) with: baseline PERG and VEP values, age, time elapsed from the diagnosis of increase in IOP (> 23 mm Hg), IOP at the time of the first diagnosis of ocular hypertension, IOP at the time of electrophysiological examination, MD, and CPSD.

In all the analyses, in order to compensate for multiple comparisons, a conservative *P*-value less than 0.01, was considered as statistically significant.

RESULTS

Displayed in Figure 1 are examples of simultaneous VEP and PERG recordings performed in 1 OAG patient treated with β-blocker monotherapy and additional treatment with Coqun (GC eye), and in 1 OAG patient treated exclusively with β-blocker monotherapy (GP eye).

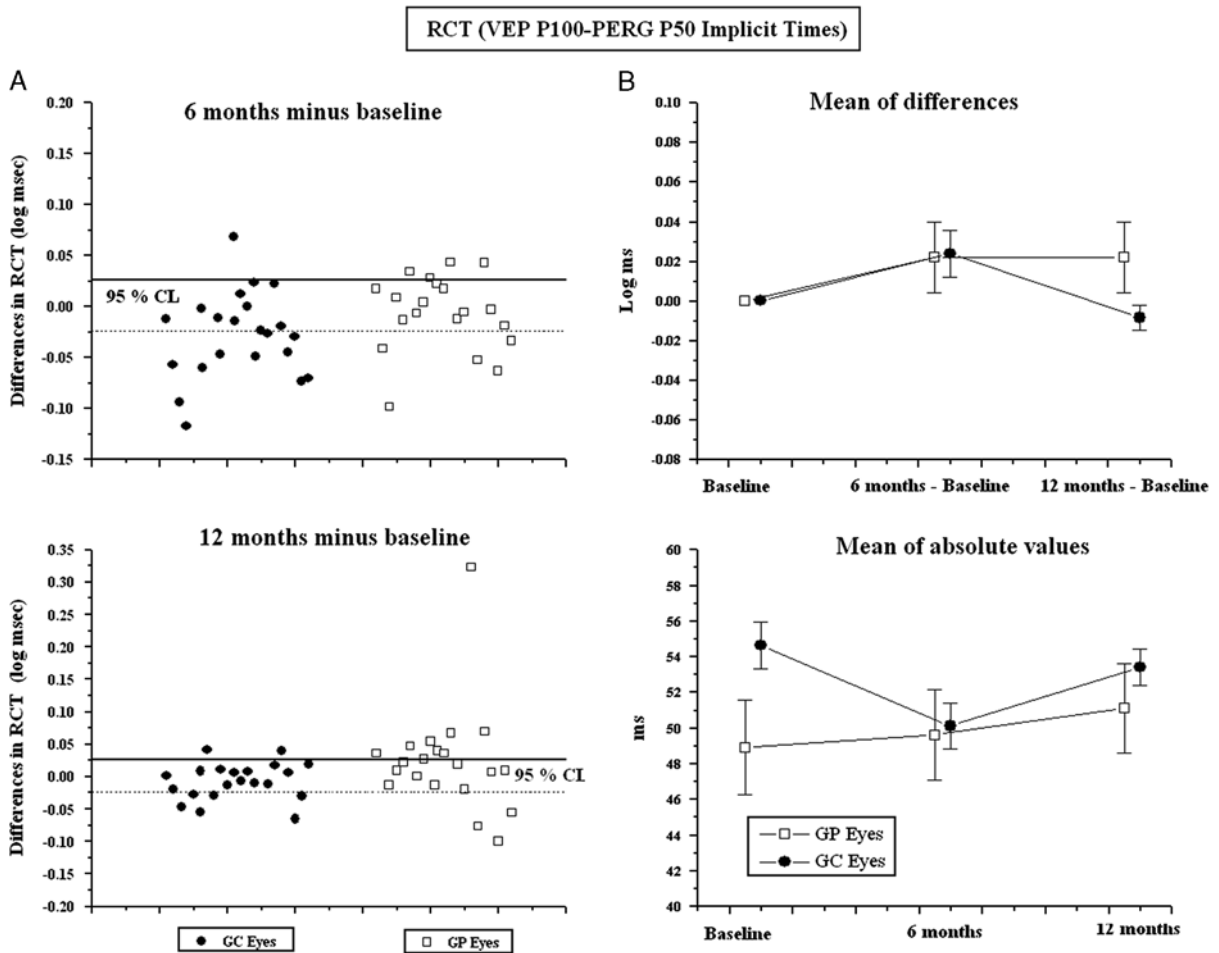Table 1 features clinical characteristics observed in control eyes and in GC and GP eyes at baseline condition.

FIGURE 6. Retinocortical Time [(RCT), difference between visual-evoked potential (VEP) P100 and pattern electroretinogram (PERG) P50 implicit times]. Individual changes (A) and graphic representation (B) of mean of differences or absolute values observed in open-angle glaucoma (OAG) patients treated with β-blocker monotherapy with additional Coqun treatment (GC eye) and in OAG patient treated exclusively with β-blocker monotherapy (GP eye). The percentage of unmodified eyes (within the 95% confidence test-retest limit), eyes with improvement (values <95% confidence test-retest limit—dashed line) and eyes with worsening (values >95% confidence test-retest limit—solid line) is reported in Table 1. The evaluation of statistical changes is reported for the differences and absolute values in Tables 2 and 3, respectively. Vertical lines—1 SEM.

Table 2 outlines the mean data of the absolute values of PERG and VEP parameters observed in controls, GC, and GP groups at baseline condition and the number of normal or abnormal GC and GP eyes.

Individual changes when compared to baseline conditions that were observed in GC and GP eyes during follow-up at 6 and 12 months are shown in Figures 2A to 6A. Figure 7 presents the correlations found in the GC eyes between the differences related to 12 months when compared to baseline and the absolute values that were detected at baseline.

Table 3 lists the number of individual changes expressed in absolute values and percentage with respect to the total number of eyes belonging to each GC and GP group.

The mean data of the differences (6 and 12 mo minus baseline conditions) and the mean data of the absolute values of PERG and VEP parameters that were observed in GC and GP groups at baseline and after 6 and 12 months, are shown in Figures 2B to 6B. The relative statistical analyses are presented in Tables 4 and 5.

When considering the individual changes concerning the 95% CL after 6 and 12 months of treatment, a large percentage (>54%) of GC eyes showed a shortening in PERG P50 implicit times and an increase in PERG P50-N95 amplitude, whereas a percentage of about 50% of GC eyes showed unmodified VEP 100 implicit times, VEP N75-P100 amplitudes, and RCT. All GC patients, in whom we observed an enhancement of VEP parameters, showed a concomitant improvement of PERG responses.

At the same time of follow-up, the majority of GP eyes presented electrophysiological parameters substantially unmodified (ie, PERG P50 implicit time within the 95% CL on 66.66% of eyes at 6 mo; P50-N95 amplitude within the 95% CL on 57.14% of eyes at 12 mo, VEP P100 implicit times within the 95% CL on 76.19% of eyes at 12 mo, N75-P100 amplitudes within the 95% CL on 47.62% eyes at 6 mo; RCT within the 95% CL on 61.90% eyes at 6 mo).

In GC eyes, the improvement in PERG P50 implicit time and P50-N95 amplitude was significantly ($P < 0.01$) related to the greatest impairment at baseline. The changes in VEP P100 implicit time and VEP N75-P100 amplitude
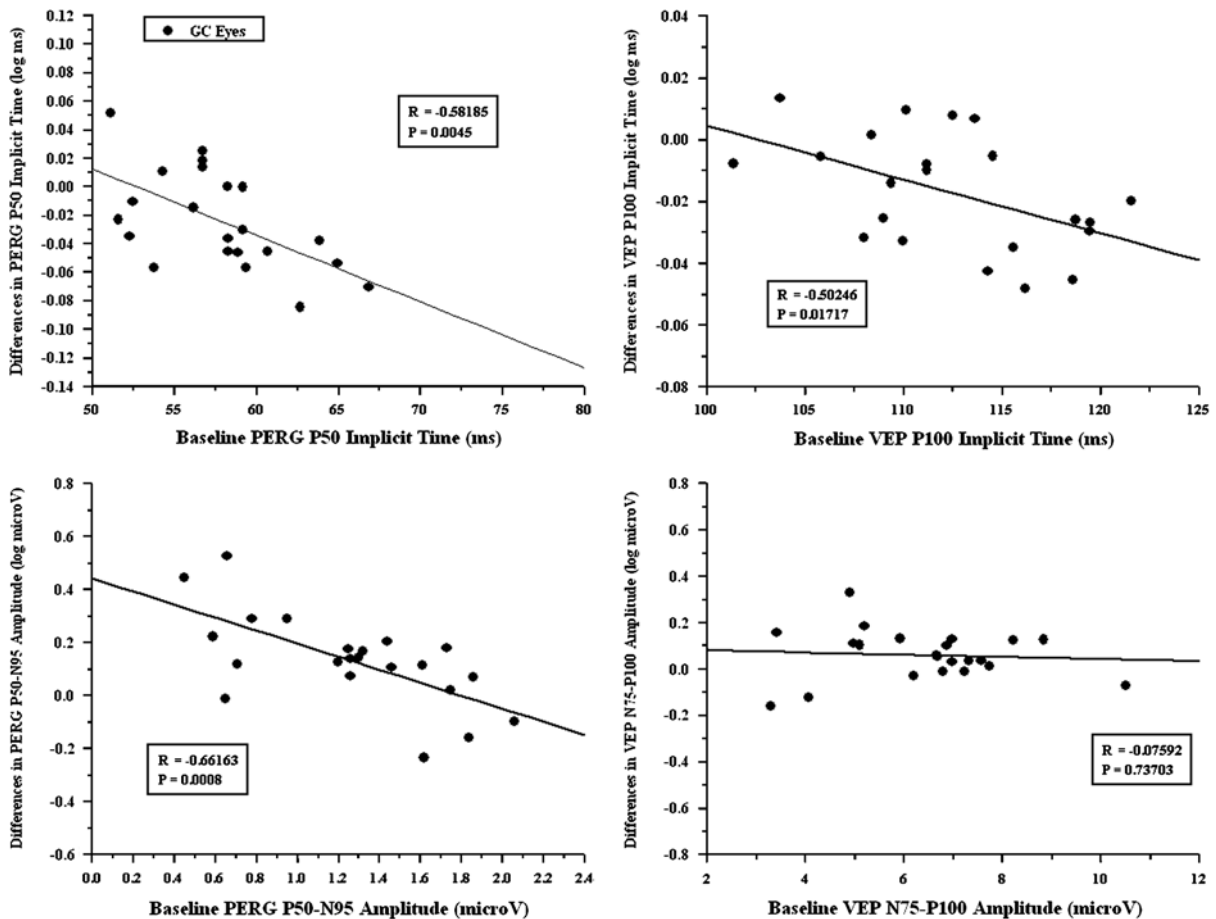
FIGURE 7. Individual pattern electroretinogram (PERG) (P50 implicit time and P50-N95 amplitude) and visual-evoked potential (VEP) (P100 implicit time and N75-P100 amplitude) values observed in open-angle glaucoma (OAG) eyes treated with coenzyme Q10 and vitamin E (Coqun, GC eyes) at baseline condition plotted as a function of the values of the corresponding differences (12 mo minus baseline). Pearson test was used for regression analysis and correlations.

were independent from the baseline condition. Over a period of 12 months, the improvement (12 mo minus baseline) of VEP implicit time was significantly correlated with the changes of PERG P50-N95 amplitude ($r = -0.66171$, $P = 0.0008$) and P50 implicit time ($r = 0.68364$, $P = 0.00045$). Nonsignificant ($P > 0.01$) correlations were observed between the differences (6 and 12 mo minus baseline) of all electrophysiological parameters (PERG, VEP, and RCT values) and age, the time elapsed from the diagnosis of increase in IOP (> 23 mm Hg), IOP at the time of the first diagnosis of ocular hypertension, IOP at the time of electrophysiological examination, MD, and CPSD.

On average, after 6 months of follow-up of the GC group, the mean values of PERG P50 and VEP P100 implicit times, and the mean values of PERG P50-N95 amplitudes, were significantly ($P < 0.01$) reduced and increased respectively when compared with those observed at baseline. Nonsignificant ($P > 0.01$) differences in VEP N75-P100 amplitudes and in RCT were found.

After 12 months of follow-up of GC eyes, the mean values of VEP P100 implicit times and the mean values of PERG P50-N95 amplitudes were significantly ($P < 0.01$) reduced and increased, respectively, when compared to those at baseline.

PERG P50 implicit times were still reduced and the change was near, without reaching, the level of significance ($P = 0.0133$).

VEP N75-P100 amplitudes and RCT values were nonsignificant ($P > 0.01$) modified with respect to the values detected at baseline condition.

When compared to baseline values, both follow-up evaluations (6 and 12 mo) for the GP eyes group showed nonsignificant ($P > 0.01$) differences in PERG P50 and VEP P100 implicit times, in PERG P50-N95 and VEP N75-P100 amplitudes and in RCT.

Throughout the entire period of treatment with Coqun, no ocular adverse side effects or significant changes in IOP (see mean values and relative statistical evaluation in Table 5) or in the visual acuity were detected in any of the patients enrolled in the study. In addition, nonsignificant ($P > 0.01$) differences in IOP between GC and GP eyes were found.

DISCUSSION

Our study aimed to evaluate whether the treatment with coenzyme Q10 in conjunction with vitamin E could have any effect on retinal function, on visual cortical

TABLE 3. Changes of Electrophysiological Parameters (PERG P50 and VEP P100 Implicit Times; PERG P50-N95 and VEP N75-P100 Amplitudes; RCT, Difference Between VEP P100 and PERG P50 Implicit Times) After 6 and 12 Months of Treatment With Respect to the Baseline Condition Observed in Open-angle Glaucoma (OAG) Patients Treated With β-Blocker Monotherapy With Additional Coqun Treatment (GC eyes) and in OAG Patients Treated Exclusively With β-Blocker Monotherapy (GP eyes)

	CG Eyes (22 Eyes)			GP Eyes (21 Eyes)		
	Unmodified	Improvement	Worsening	Unmodified	Improvement	Worsening
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
PERG P50 IT 6 mo	7 (31.81)	13 (59.09)	2 (9.10)	14 (66.66)	2 (9.52)	5 (23.82)
PERG P50 IT 12 mo	6 (27.27)	14 (63.63)	2 (9.10)	12 (57.14)	2 (9.53)	7 (33.33)
PERG P50-N95 A 6 mo	8 (36.36)	14 (63.64)	0 (0)	9 (42.85)	5 (23.82)	7 (33.33)
PERG P50-N95 A 12 mo	9 (40.90)	12 (54.55)	1 (4.55)	12 (57.14)	4 (19.04)	5 (23.82)
VEP P100 IT 6 mo	12 (54.55)	9 (40.90)	1 (4.55)	19 (90.48)	0 (0)	2 (9.52)
VEP P100 IT 12 mo	12 (54.55)	10 (45.45)	0 (0)	16 (76.19)	0 (0)	5 (23.81)
VEP N75-P100 A 6 mo	11 (50)	8 (36.36)	3 (13.64)	10 (47.62)	2 (9.53)	9 (42.85)
VEP N75-P100 A 12 mo	9 (40.90)	11 (50)	2 (9.10)	6 (28.57)	4 (19.04)	11 (52.39)
RCT 6 mo	11 (50)	10 (45.45)	1 (4.55)	13 (61.90)	5 (23.82)	3 (14.28)
RCT 12 mo	15 (68.18)	5 (22.72)	2 (9.10)	10 (47.62)	3 (14.29)	8 (38.09)

Unmodified = within the 95% confidence test-retest limit; improvement = values of increase in amplitudes (A) and shortening in implicit times (IT) that exceeded the 95% confidence test-retest limit; worsening = values of reduction in amplitudes (A) and increase in implicit times (IT) that exceeded the 95% confidence test-retest limit. N = number of eyes.

PERG indicates pattern electroretinogram; RCT, Retinocortical Time; VEP, visual-evoked potential.

responses and on neural conduction along the postretinal visual pathways in OAG patients.

Retinal Function (PERG Data)

Glaucomatous retinal dysfunction was assessed by PERG recordings. Given that in OAG loss of ganglion cells and their fibers has been documented by histologic studies[36–38] and by objective methods of "in vivo" morphologic evaluation of retinal fibers,[39,40] the impaired PERG responses observed in OAG patients could be ascribed to a dysfunction of the innermost retinal layers,[2–6] although a functional impairment of preganglionic elements has also been suggested.[1,41–44]

In the present study, we observed how the group of OAG patients treated over a 12-month period with Coqun (coenzyme Q10 and vitamin E TPGS 500, GC eyes), showed an improvement of retinal bioelectric responses as suggested by the increase of PERG amplitudes and by the

TABLE 4. Mean Values of the Individual Differences (6 Months Minus Baseline and 12 Months Minus Baseline) in PERG P50 and VEP P100 Implicit Times, PERG P50-N95 and VEP N75-P100 Amplitudes, and in the RCT Observed in Open-angle Glaucoma (OAG) Patients Treated With β-Blocker Monotherapy With Additional Coqun Treatment (GC eyes) and in OAG Patients Treated Exclusively With β-Blocker Monotherapy (GP eyes)

	6 mo-Baseline			12 mo-Baseline		
	Mean	SD	ES	Mean	SD	ES
Difference in PERG P50 implicit time (Log ms)						
GC eyes (N = 22)	−0.02826	0.0327	0.00698	−0.0242	0.0343	0.00731
GP eyes (N = 21)	0.00904	0.0311	0.00678	0.0161	0.0350	0.00764
ANOVA GC vs. GP ($F_{1,42}$) =	14.7; $P < 0.0001$			14.5; $P = 0.0005$		
Difference in PERG P50-N95 amplitude (Log µV)						
GC eyes (N = 22)	0.1374	0.141	0.0300	0.1302	0.174	0.0370
GP eyes (N = 21)	−0.0375	0.257	0.0560	−0.0104	0.163	0.0346
ANOVA GC vs. GP ($F_{1,42}$) =	7.78; $P = 0.0080$			3.69; $P = 0.009$		
Difference in VEP P100 implicit time (Log ms)						
GC eyes (N = 22)	−0.01744	0.0212	0.00452	−0.0171	0.0186	0.00397
GP eyes (N = 21)	0.00850	0.0265	0.00578	0.0182	0.0316	0.00690
ANOVA GC vs. GP ($F_{1,42}$) =	12.6; $P = 0.0010$			20.0; $P < 0.0001$		
Difference in VEP N75-P100 amplitude (Log µV)						
GC eyes (N = 22)	0.0532	0.116	0.0248	0.0587	0.108	0.0229
GP eyes (N = 21)	−0.0568	0.127	0.0276	−0.0609	0.161	0.0351
ANOVA GC vs. GP ($F_{1,42}$) =	8.84; $P = 0.0049$			8.28; $P = 0.0063$		
Difference in RCT (VEP P100-PERG P50 implicit times, Log ms)						
GC eyes (N = 22)	0.0239	0.0547	0.0117	−0.00853	0.0293	0.00624
GP eyes (N = 21)	0.0218	0.0819	0.0179	0.02176	0.0819	0.01788
ANOVA GC vs. GP ($F_{1,42}$) =	0.0106; $P = 0.9185$			2.65; $P = 0.1109$		

ANOVA indicates statistical evaluation by a 1-way analysis of variance between the GC and GP eyes; ES, 1 SEM; PERG, pattern electroretinogram; RCT, Retinocortical Time; SD, 1 mean SD; VEP, visual-evoked potential.

TABLE 5. Mean Values of the Absolute Values of PERG P50 and VEP P100 Implicit Times, PERG P50-N95 and VEP N75-P100 Amplitudes, of the RCT, and of the Intraocular Pressure Detected at Baseline Condition After 6 and 12 Months of Treatment Observed in Open-angle Glaucoma (OAG) Patients who Were Treated With Coenzyme Q10 Plus Vitamin E (GC Eyes) and in Untreated OAG Eyes (GP Eyes)

	Mean	SD	ES	ANOVA Versus Baseline	ANOVA Versus GP Eyes
PERG P50 implicit time (ms)					
GC eyes (N = 22)					
Baseline	57.9	4.29	0.914		$F_{1,42} = 0.07; P = 0.800$
6 mo	54.2	3.89	0.830	$F_{1,43} = 8.75; P = 0.0051$	$F_{1,42} = 17.51; P < 0.001$
12 mo	54.7	3.78	0.807	$F_{1,43} = 6.68; P = 0.0133$	$F_{1,42} = 22.73; P < 0.001$
GP eyes (N = 21)					
Baseline	58.2	3.34	0.729		
6 mo	59.5	4.41	0.963	$F_{1,41} = 1.14; P = 0.2928$	
12 mo	60.4	4.06	0.887	$F_{1,41} = 3.75; P = 0.0600$	
PERG P50-N95 amplitude (mV)					
GC eyes (N = 22)					
Baseline	1.26	0.468	0.0997		$F_{1,42} = 0.20; P = 0.657$
6 mo	1.71	0.634	0.1351	$F_{1,43} = 7.28; P = 0.0100$	$F_{1,42} = 9.06; P = 0.004$
12 mo	1.66	0.498	0.1063	$F_{1,43} = 7.35; P = 0.0097$	$F_{1,42} = 8.55; P = 0.006$
GP eyes (N = 21)					
Baseline	1.33	0.556	0.121		
6 mo	1.18	0.511	0.111	$F_{1,41} = 0.830; P = 0.3678$	
12 mo	1.22	0.488	0.106	$F_{1,41} = 0.514; P = 0.4775$	
VEP P100 implicit time (ms)					
GC eyes (N = 22)					
Baseline	112.4	5.38	1.15		$F_{1,42} = 3.50; P = 0.069$
6 mo	108.0	5.47	1.17	$F_{1,43} = 7.29; P = 0.0100$	$F_{1,42} = 0.17; P = 0.687$
12 mo	108.1	4.92	1.05	$F_{1,43} = 7.80; P = 0.0078$	$F_{1,42} = 1.74; P = 0.195$
GP eyes (N = 21)					
Baseline	107.1	12.1	2.63		
6 mo	109.1	11.4	2.50	$F_{1,41} = 0.312; P = 0.5793$	
12 mo	111.5	11.0	2.40	$F_{1,41} = 1.54; P = 0.2216$	
VEP N75-P100 amplitude (mV)					
GC eyes (N = 22)					
Baseline	6.43	1.74	0.371		$F_{1,42} = 0.001; P = 0.981$
6 mo	7.46	2.41	0.514	$F_{1,43} = 2.60; P = 0.1146$	$F_{1,42} = 2.92; P = 0.095$
12 mo	7.51	2.25	0.480	$F_{1,43} = 3.14; P = 0.0838$	$F_{1,42} = 3.71; P = 0.061$
GP eyes (N = 21)					
Baseline	6.46	4.57	0.998		
6 mo	5.78	3.90	0.851	$F_{1,41} = 0.271; P = 0.6057$	
12 mo	5.71	3.73	0.813	$F_{1,41} = 0.334; P = 0.5663$	
RCT (VEP P100-PERG P50 implicit times, ms)					
GC eyes (N = 22)					
Baseline	54.6	6.19	1.32		$F_{1,42} = 3.78; P = 0.059$
6 mo	50.1	6.09	1.30	$F_{1,43} = 5.68; P = 0.0218$	$F_{1,42} = 0.03; P = 0.859$
12 mo	53.4	4.81	1.02	$F_{1,43} = 0.506; P = 0.4807$	$F_{1,42} = 0.76; P = 0.390$
GP eyes (N = 21)					
Baseline	48.9	12.2	2.66		
6 mo	49.6	11.6	2.53	$F_{1,41} = 0.0406; P = 0.8414$	
12 mo	51.1	11.4	2.49	$F_{1,41} = 0.366; P = 0.5484$	
Intraocular pressure (mm Hg)					
GC eyes (N = 22)					
Baseline	15.7	1.92	0.41		$F_{1,42} = 1.14; P = 0.292$
6 mo	15.9	1.72	0.37	$F_{1,43} = 0.13; P = 0.718$	$F_{1,42} = 1.10; P = 0.300$
12 mo	16.2	1.69	0.36	$F_{1,43} = 0.84; P = 0.364$	$F_{1,42} = 0.30; P = 0.585$
GP eyes (N = 21)					
Baseline	16.3	1.76	0.38		
6 mo	16.5	2.02	0.44	$F_{1,41} = 0.12; P = 0.734$	
12 mo	15.9	1.88	0.41	$F_{1,41} = 0.51; P = 0.481$	

ANOVA indicates statistical evaluation by a 1-way analysis of variance versus GP eyes at baseline condition and in GC and GP eyes at different times of evaluation (6 and 12 mo) with respect to the baseline condition; ES, 1 SEM; PERG, pattern electroretinogram; RCT, Retinocortical Time; SD, 1 mean SD; VEP, visual-evoked potential.

reduction of implicit times. This increase was significantly different from the group of GP eyes (OAG patients only treated with β-blockers).

The possible mechanisms of action of coenzyme Q10 leading to the PERG observed changes, can be explained on the basis of experimental models. In fact, Nucci et al[24] observed how in rats with experimental ocular hypertension, the administration of coenzyme Q10 prevented the glutamate-induced apoptosis of retinal ganglion cells. In this report,[24] as well as in the present study, the rationale using coenzyme Q10 was based on the evidence that oxidative stress, related to defective energy metabolism, may

play an important role in the glaucomatous retinal ganglion cell loss.[23] It is known that the mitochondrial function (mitochondrial electron transport chain and mitochondrial calcium homeostasis[45–47]), together with the inhibition of key enzymes of the tricarboxylic acid cycle, is involved in the neuronal cell death that may be protected by coenzyme Q10.[48]

In this way, coenzyme Q10 was suggested,[49] as it was believed to have a useful effect for several human pathologies (based on mitochondrial functional deficit such as mitochondrial myopathies, cardiovascular diseases, Friedreich ataxia, migraine).

Coqun contains coenzyme Q10 associated with vitamin E TPGS. Because of the lack of scientific evidence regarding the role of vitamin E on the ganglion cell function, the effects derived from the combined use of coenzyme Q10 plus vitamin E TPGS, also need to be considered as a possible explanation of our results.

The changes in PERG responses (increase in amplitude and reduction of implicit time when compared to the baseline) observed in GC eyes were not found in all patients treated with Coqun (coenzyme Q10 100 and vitamin E TPGS 500), but only in a percentage of about 60% (54.54% for P50-N95 amplitude and 63.63% for P50 implicit time). In order to detect patients featuring a potential effect on the ganglion cell function, we correlated the PERG differences with several parameters (age, time elapsed from the diagnosis of increase in IOP, IOP at the time of the first diagnosis of ocular hypertension, IOP at the time of electrophysiological examination, MD, and CPSD) and none of these correlations reached a significant level, thereby leading to the conclusion that none of these parameters influence the improvement of the retinal function after coenzyme Q10 treatment. By contrast, a significant correlation was detected between the values of the PERG baseline and the relative differences (12 mo minus baseline), thus suggesting that the patients who "better responded" to the coenzyme Q10 supplementation were those who at baseline, displayed the greater retinal dysfunction.

In our study, we did not perform any morphologic examination, and thus, although our results indicate an improvement of bioelectrical retinal activity, we were not able to demonstrate whether there were other effects on the retinal fiber structure (ie, an increase in the retinal nerve fiber layer thickness).

It is also known that an improvement of PERG responses may be obtained by lowering the IOP.[12–17] During the entire period of treatment, GC patients showed nonsignificant changes in IOP. Therefore, it can be excluded that the above-reported ganglion cell function improvement may be related to IOP changes.

Visual Cortical Responses (VEP Data)

In OAG patients who were treated with Coqun during a 12-month period, we observed an improvement of bioelectric cortical responses as suggested by the increase in VEP amplitudes (only in the average of individual differences but not in the average of absolute values) and by the shortening in VEP implicit times. This increase was significantly different from the group of GP eyes.

Glaucomatous VEP abnormalities have been ascribed to a dysfunction of the innermost retinal layers (ganglion cells and their fibers) associated with a delay in neural conduction along postretinal visual pathways.[7] In order to explain the influence of Coqun in VEP responses, the effects

on retinal function and on neural conduction in postretinal visual pathways may be considered separately. The first was discussed above, whereas the latter is clarified as follows (see RCT data).

The individual changes of the VEP enhancement was observed in a percentage of about 50% (50% for N75 amplitude and 45.45% for P100 implicit time) of patients treated with Coqun. These changes are independent from the baseline condition, several demographic or glaucomatous parameters (see above). We only detected that the VEP enhancement was observed in those GC patients on which a concomitant improvement in PERG responses was found. In fact, over a period of 12 months the improvement of VEP implicit time was significantly correlated with the changes of PERG P50-N95 amplitude and P50 implicit time.

Therefore, following the Coqun treatment, it can be suggested that the presence of better cortical responses depends on the reduction of the ganglion cell dysfunction.

Neural Conduction Along Postretinal Visual Pathways (RCT Data)

The aim of our study was also to evaluate the effect of coenzyme Q10 in neural conduction along postretinal visual pathways. We evaluated the changes of an "electrophysiological index" derived from the difference between VEP P100 and PERG P50 implicit times, known as "RCT."[27,33]

In OAG patients, abnormal RCT related to retinal dysfunction (PERG-reduced amplitudes) was previously described.[7,50] RCT is not able to selectively differentiate a single structural dysfunction of the postretinal visual pathways [ie, optic chiasm, lateral geniculate nucleus (LGN), optic radiation[27]; yet, an explanation regarding the delay in RCT in OAG patients may be presented through the available data reporting the effects of glaucoma at the dorsal LGN (dLGN) level. In fact, structural and functional damage in the dLGN of subjects or animals affected by a well-documented glaucomatous optic neuropathy has been reported.[51–53] An impairment at the dLGN level could cause functional changes in those cells producing visual cortical-evoked responses; this is likely to be related to the delay and to the reduction of the VEP responses observed in our OAG patients.

During a 12-month period of study, it was observed that a large percentage of both GC and GP patients showed unmodified RCT, and nonsignificant differences were found between the RCT values observed in the GC and GP groups. All this led us to believe that the treatment with coenzyme Q10 plus vitamin E is not able to improve the neural conduction along the postretinal visual pathways notwithstanding the effect of the retinal structures (improvement in PERG responses). Our data differ from those obtained by citicoline treatment that not only induced an enhancement of retinal function (improvement in PERG responses) and of bioelectrical cortical responses (improvement in VEPs responses), but also a reduction in the delay of neural conduction along the postretinal visual pathways (shortening in RCT).[19–21] Nevertheless, the mechanisms of action of citicoline are well different from those of coenzyme Q10, and in particular a neuromodulator effect was also suggested for the neural conduction.[21]

CONCLUSIONS

Our results suggest that coenzyme Q10, in conjunction with vitamin E treatment, may induce an enhancement in PERG responses in OAG patients. Therefore, a possible effect of coenzyme Q10 on the innermost (ganglion cells and their fibers) retinal layers function of OAG patients can be assumed. A possible effect of interaction between coenzyme Q10 and vitamin E cannot be entirely excluded. To clarify this potential confounding factor, a clinical trial administrating coenzyme Q10 orally, with or without vitamin E, should be required in the future.

As in our cohort of glaucoma subjects it was necessary to include those with "no previous history or presence of any disease involving cornea, lens, macula, or retina," we enrolled patients who were not very old, and aged between 42 and 60 years. Considering all that may influence the electrophysiological responses (ie, cataract or maculopathy) we believe that a similar study performed in older patients may present several confounding factors. At present, we are not able to determine whether the Coqun would produce the same observed effect in an older population of OAG patients.

An important question may be raised on the concentration of coenzyme Q10 at the retinal level after the administration of eye drops. This is actually unidentified, but it can be useful to know that in patients undergoing vitrectomy in whom Coqun eye drops were administered 1 hour before surgery, the presence of coenzyme Q10 was detectable in the vitreous (mean of tested eyes: $0.528 \pm 0.769\,\mu g/mL$). In the same patients, coenzyme Q10 content in plasma was similar to that observed in the control group of patients undergoing vitrectomy but without administration of Coqun.[54]

In conclusion, coenzyme Q10 in association with vitamin E treatment induces a beneficial effect on glaucomatous retinal function (PERG improvement). As the differences in VEP responses were related to the PERG improvement, the enhancement of the visual cortical responses can be ascribed to the effect of coenzyme Q10 in conjunction with vitamin E on retinal structures.

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