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Electrophysiological evaluation of the macular cone adaptation: VEP after photostress

A review

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Abstract. In the present review, the methodologies and clinical applications of the visual evoked potentials (VEPs) after photostress, will be described. Photostress induces transient VEP changes consisting of an increase in response latency and a decrease in amplitude. When serial VEP recordings are obtained at discrete time intervals (i.e., every 20 s) after bleaching, the recovery of VEP waveform can be evaluated. The time needed for the VEP to recover to the pre-bleach, baseline status (recovery time after photostress) ranges in normal subjects between 68 and 78 s. Patients with different pathologies (maculopathies, ocular hypertension and glaucoma, diabetes with or without retinopathy, multiple sclerosis with optic neuritis) showed an abnormal response after photostress (higher increase in latency and decrease in amplitude and longer recovery time) with respect to age-matched controls. Our results indicate that the VEPs after photostress represent an objective, although not specific, index of the dynamic properties of macular performance after exposure to intense light stimulation.

Key words: visual evoked potential, photostress, maculopathy, glaucoma, diabetes, multiple sclerosis

Introduction

Several psychophysical techniques (see, for example, Weleber and Eisner [1]) have been developed in the clinical setting to evaluate the macular function: color matching techniques, absolute cone thresholds, cone sensitivity to sinusoidal flicker modulated at different temporal frequencies (i.e., the De Lange function), perimetric cone sensitivity tested by microperimetric techniques, recovery of visual acuity after photostress.

Recently, two electrophysiological tests namely the *focal electroretinogram* and the *visual evoked potentials after photostress* have been receiving increasing attention because they are objective and direct probes of macular function [2].

These techniques provide somewhat complementary results about macular function: one in 'steady-state' conditions (i.e., the focal electroretinogram), the other in a 'dynamic' status due to the recovery of the system after ex-

posure to a bleaching light (i.e., visual evoked potentials after photostress) [2].

Visual evoked potentials (VEP) after photostress, as originally suggested by Lovasik [3] and Franchi et al. [4], may represent an electrophysiological application of the macular photostress test (MPST) proposed by Baillart [5]. The MPST measures the period of recovery in visual acuity after dazzling of the macular region with an ophthalmoscope; it was indicated as an index of the 'functional macular reserve' [5], has been applied to normal subjects [6, 7], and has been found to be significantly altered in several macular disorders, including the early stages of age-related macular degeneration [8–11], diabetic retinopathy [8, 12, 13] or glaucoma [14]. The test has proven to be sufficiently reliable and clinically useful to detect early dysfunction.

Photostress induces transient VEP changes consisting of an increase in response latency and a decrease in amplitude. When serial VEP recordings are obtained at discrete time intervals (i.e., every 20 s) after bleaching, the recovery of VEP waveform can be evaluated. The time needed for the VEP to recover to the pre-bleach, baseline status, is considered as 'Recovery time after photostress'.

Methodological procedures

The three fundamental steps in performing the VEP after photostress test are the following [15–21]: (a) recording of 'basal VEP'; (b) dazzling of the central retina; (c) recording of VEPs after dazzling and evaluation of the recovery time after photostress.

(a) Recording of 'basal VEP'

The subjects under examination are seated in a semi-darkened room, acoustically isolated, in front of a display, which is surrounded by a uniform field with a luminance of 5 cd/m^2. Prior to the experiment, each subject has been adapted to the ambient room light for 10 min, with a natural pupil (diameter of about 5 mm). The stimulation is monocular, after full occlusion of the fellow eye.

The visual stimuli consist of checkerboard patterns (contrast, 70%; mean luminance, 100 cd/m^2) generated on a TV monitor and reversed in contrast at the rate of two reversals/s. At the viewing distance of 114 cm, the single check edge subtends 15 min of visual arc. The screen of the monitor subtends 18° and, in order to maintain stable fixation, a small red target (0.5°) is placed in the center of the stimulation field.

Cup-shaped electrodes of Ag/AgCl are fixed with collodion in the following positions: active electrode in Oz, reference electrode in Fpz; ground in left arm. The interelectrode resistance is kept below 3 kΩ. VEP signals are amplified (gain 20 000), filtered (bandpass 1–100 Hz), sampled with 12-bit resolution, and averaged with automatic artifact rejection.

The recording session begins with a preliminary experiment in which at least two VEPs are recorded (analysis time 500 ms, averaging over 100 stimulus periods), and the loss in recording time due to artifacts is noted. The resulting waveforms are stored and superimposed to check for the repeatability of the results. The VEP response is characterized by several waves with three peaks of negative–positive–negative polarity, respectively. In normal subjects, these peaks have the following times-to-peak (peak latency): 75, 100 and 145 ms. After this preliminary trial, the basal VEPs are recorded by reducing the average to 40 events per trial. Responses are accepted only if no more than two sweeps are discarded because of artifacts. The basal VEP waveform is kept on display on the computer screen. Six consecutive records are taken every 20 s, and the corresponding records are compared to the basal response in order to check intratest reproducibility.

(b) Dazzling of the central retina

Photostress is induced for a duration of 30 s by means of a circular diffusing surface (the bulb of a 200-W lamp). Subjects fixate at the center of the circular surface from a distance of 20 cm. The bleaching lamp usually produces a central relative scotoma of 6° in diameter. During the photostress procedure the pupil diameter is usually about 2 mm.

(c) Recording of VEP after dazzling and evaluation of the recovery time after photostress

Immediately following bleaching, the subject was asked to fixate at the center of the pattern stimulus (in correspondence of the fixation target) and the VEP recording was started. The small red target was perceived by all subjects and patients, notwithstanding the presence of a subjective scotoma. Several consecutive records (n=4 to n=9, depending on the subject or patient) were obtained, each 20 s in length, and stored on the computer screen. Recording was continued until the response waveform was superimposable upon the baseline record. When this condition was obtained, the recording was stopped and the corresponding time (measured by a digital clock incorporated into the computer analysis software) was considered as 'recovery time after photostress (RT)'. For example, in a patient in which an RT of 96 s was observed,

we performed five consecutive records: four of 20 s (40 events averaged for each record) and the last of 16 s (32 events averaged).

(d) Noise evaluation

In each subject or patient, the signal-to-noise ratio (SNR) of the VEP response was assessed by measuring a 'noise' response while the subject fixated at an unmodulated field of the same mean luminance as the stimulus. Two noise record were measured: one of 40 events and another of a number of events corresponding to those averaged in the last record (see above). Both records were obtained immediately after the end of the bleaching protocol. The two noise peak-to-peak amplitudes were measured in a temporal window corresponding to that at which the response component of interest (i.e., N75-P100) was expected to peak. SNRs for this component were determined, either in the short or long averaging record, by dividing the peak amplitude of the component by the noise in the corresponding temporal window. In all subjects and patients, the VEP SNRs, determined in both ways, were ≥ 2 in all the steps of the experimental procedure.

Clinical applications of VEP after photostress

The curve responses of VEP recordings after photostress (changes in P100 peak latency and in N75-P100 peak amplitude) in normal subjects and in several pathological conditions are shown in Figure 1.

In normal subjects as in patients with several disorders, at 20 s after photostress, an increase in P100 peak latency and a decrease in N75-P100 peak amplitude has been observed. At 40 and 60 s after photostress the P100 peak latencies are shorter than the 20 s value, but still longer than in the basal P100 peak latency. The N75-P100 peak amplitude increases from the value observed at 20 s, but without reaching the basal value. Therefore, in the analysis of VEP after photostress the following parameters are usually considered: the mean increment in P100 peak latency (MLI), the mean percentage decrease in N75-P100 amplitude (MPAD) observed at 20, 40 and 60 s after dazzling and RT.

In normal subjects (age range, 26–56 years) the VEPs are superimposable to the baseline condition (RT) between 68 and 80 s [15–21].

(a) Subjects with maculopathies

VEP after photostress were assessed in patients with different maculopathies: age-related, Stargardt's disease, Best's disease, cone dystrophy (Parisi, 2001,

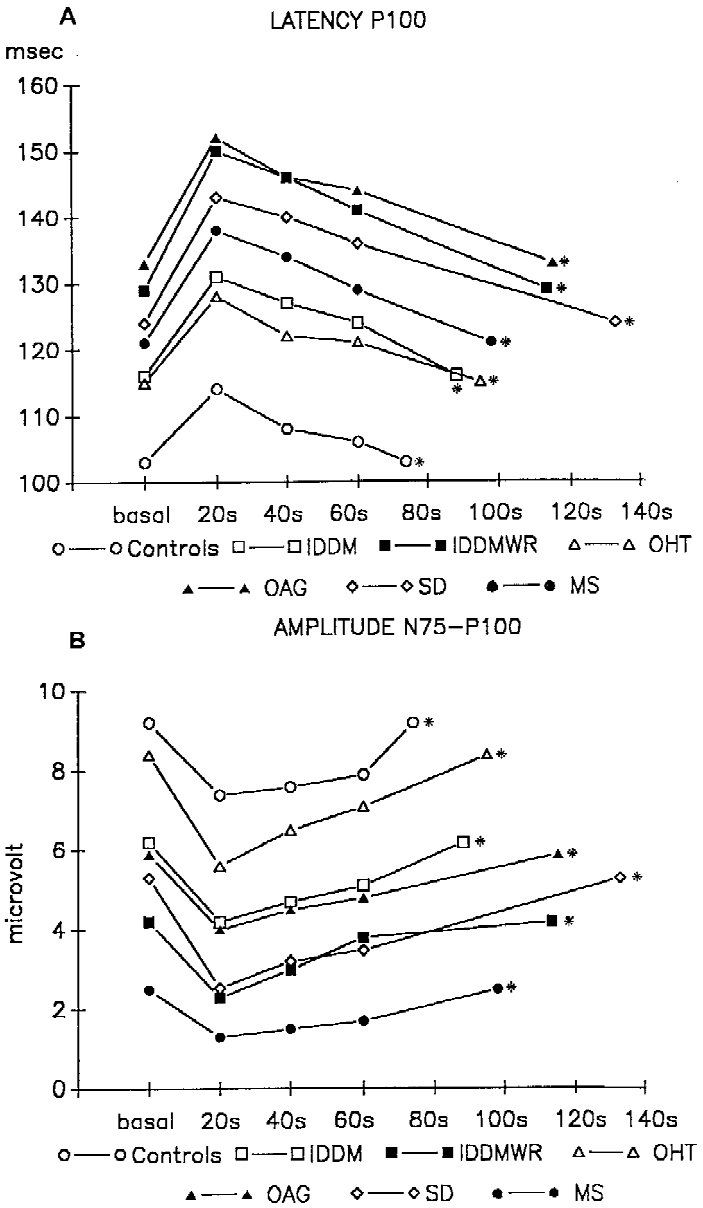

Figure 1. Graphic representation of mean values of the VEP P100 peak latency (A) and N75-P100 peak-to-peak amplitude (B) observed in normal subjects (Controls), in diabetic patients with (IDDMWR) or without (IDDM) retinopathy, in patients with ocular hypertension (OHT) or open angle glaucoma (OAG), in patients with Stargardt's disease (SD), in multiple sclerosis patients previously affected by optic neuritis (MS). The mean values refer to the basal condition and to 20, 40, 60 s after photostress. The standard deviation of the P100 latency values was 3–5% of the mean value of controls and 5–8% of the mean value of patients; the standard deviation of the N75-P100 amplitude values was 7–9% of the mean value of controls and 10–12% of the mean value of patients. The last symbol represents the mean recovery time after photostress (*).

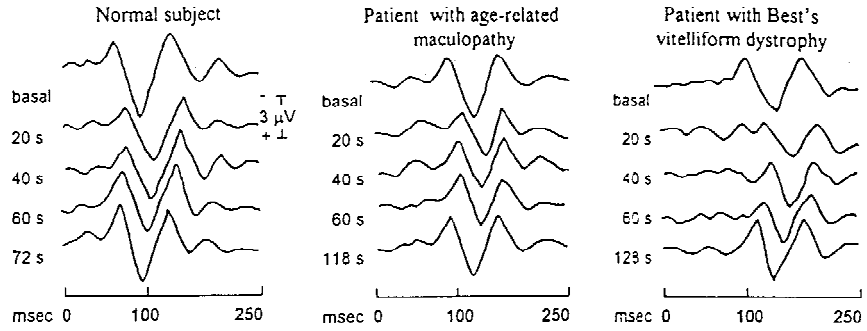

Figure 2. Examples of VEP recorded in the basal condition and 20, 40, 60 s after photostress in a normal subject and in patients with two different maculopathies. In each recording series, the last VEP waveform is superimposable on the basal record and the corresponding time is considered as RT.

in preparation). In all patients with maculopathies, the basal VEP showed a delay in P100 latency and a reduction in N75-P100 amplitude.

After photostress, all patients showed higher MLI and more marked MPAD than in age-matched control subjects. In addition, an RT longer than in age-matched controls (mean 114±2 s) was observed.

Examples of VEPs after photostress recorded in a normal subject and in patients with maculopathies are shown in Figure 2.

(b) Diabetes: newly diagnosed, without retinopathy and with retinopathy

Persons with Type I (insulin-dependent) diabetes have been extensively studied by recordings of VEP after photostress.

In fact, in a first study we examined age-matched diabetic patients with or without fluorangiographic signs of retinopathy [16]; subsequently, we studied diabetic patients with a duration of disease less than 6 months [17, 18]; finally, we assessed VEP after photostress responses in relation with the duration of the disease and the metabolic control [19].

Newly diagnosed diabetic patients (mean duration of disease less than 6 months), without retinopathy (duration of disease between 1 and 20 years and no fluorangiographic signs of retinopathy) and with background retinopathy (Klein level 3–5), displayed basal VEPs with delayed P100 latency and reduced N75-P100 amplitude, with respect to the values observed in age-matched controls [16–19].

The VEP responses after photostress in newly diagnosed diabetics were similar to those of age-matched controls (RT, 73.6±1.2 s), while impaired responses were observed in diabetics with or without retinopathy. In diabetic patients with and without retinopathy, higher MLI, more marked MPAD and

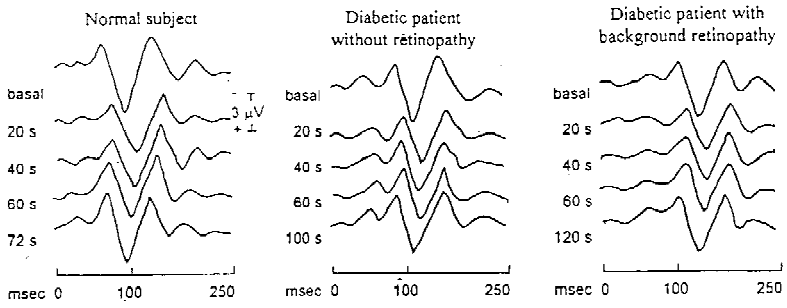

Figure 3. Examples of VEP recorded in the basal condition and 20, 40, 60 s after photostress in a normal subject and in diabetic patients without retinopathy or with a background retinopathy. In each recording series, the last VEP waveform is superimposable on the basal record and the corresponding time is considered as RT.

delayed RT (no retinopathy patients: 88.17±10.48 s; retinopathic patients: 113.33±12.9 s) were found, when compared with those of age-matched controls. No correlations between duration of disease or metabolic control parameters, and MLI, MPAD and RT were observed [16–19].

Examples of VEPs after photostress recorded in a normal subject and in diabetic patients without retinopathy or with a background retinopathy are shown in Figure 3.

(c) Artificially increased intraocular pressure, ocular hypertension and primary open angle glaucoma

VEP after photostress responses have been assessed in an experimental condition of ocular hypertension, in patients with ocular hypertension (OHT) and in patients with primary open angle glaucoma (POAG).

In order to evaluate the effects of acutely raised IOP on the VEP after photostress responses, the IOP was increased up to a value equal to half the systolic arterial pressure. Artificially increased intraocular pressure (IOP) was obtained in normal subjects by using a Baillart ophthalmodynamometer. The results showed that transient IOP elevation induces changes on the VEP response after photostress: higher MLI, more marked MPAD and longer RT (114.2±5.1 s), when compared to a condition of normal IOP [20].

Reduced basal VEP N75-P100 amplitudes were found in POAG patients, while delayed basal VEP P100 latency was found in both POAG and OHT patients, with respect to control subjects.

The VEP responses after photostress were impaired in both OHT and POAG patients: higher MLI, more marked MPAD and longer mean RT (OHT, 95.1±6.5 s; POAG, 113.2±11.8 s) were observed in patients when compared to control subjects [15].

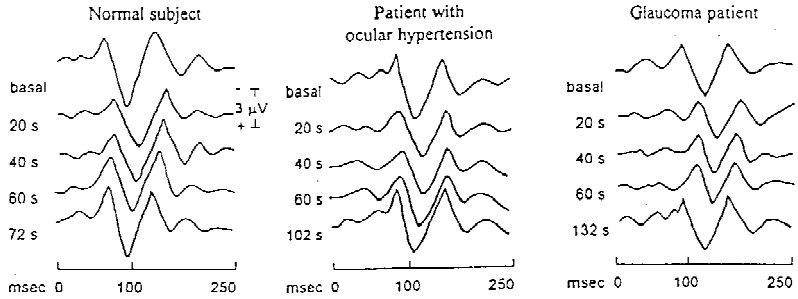

Figure 4. Examples of VEP recorded in the basal condition and 20, 40, 60 s after photostress in a normal subject and in patients with ocular hypertension or glaucoma. In each recording series, the last VEP waveform is superimposable on the basal record and the corresponding time is considered as RT.

Examples of VEPs after photostress recorded in a normal subject and hypertension or open angle glaucoma are shown in Figure 4.

(d) Multiple sclerosis patients with or without optic neuritis

Recordings of VEP in the basal condition and after photostress have been performed in multiple sclerosis patients previously affected by optic neuritis (but with complete recovery of the visual acuity and with at least 12 months elapsed form the last optic neuritis episode (MSON)) or without a history of optic neuritis (MSWO).

In MSON and MSWO patients, basal VEP P100 latencies and N75-P100 amplitudes were delayed and reduced, respectively, when compared with those of age-matched controls.

VEP recorded after photostress in MSWO patients showed MLI, MPAD and RT (71.2±4.7 s) similar to those of controls, while MSON patients displayed higher MLI, more marked MPAD and longer RT (97.8±5.1 s) when compared to control values [21].

Examples of VEPs after photostress recorded in a normal subject and in multiple sclerosis patients with or without optic neuritis are shown in Figure 5.

(e) Carotid occlusive disease

VEPs after photostress have been investigated in carotid occlusive disease by Bianchini et al. [22] and Franchi et al. [23]. It was found that an improvement of the response amplitude after photostress paralleled the restoration of cerebral blood flow following endoarterectomy.

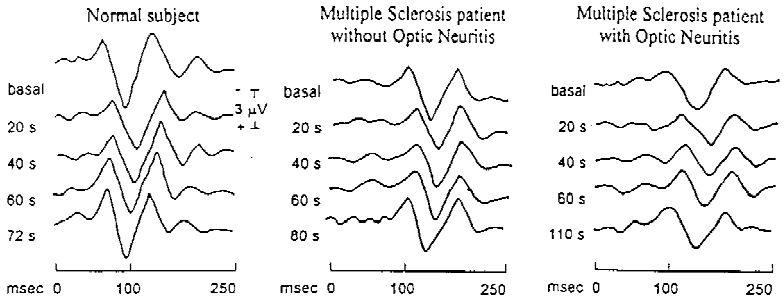

Figure 5. Examples of VEP recorded in the basal condition and 20, 40, 60 s after photostress in a normal subject and in multiple sclerosis patients with or without optic neuritis. In each recording series, the last VEP waveform is superimposable on the basal record and the corresponding time is considered as RT.

Concluding remarks

In patients with macular degeneration, diabetes, or glaucoma, the results obtained evaluating the recovery of visual acuity after photostress [8–14] are consistent with those observed by the assessment of the recovery of visual cortical electrophysiological responses after dazzling of the central retina [15–20]. Since patients with an impairment of the optic nerve (newly diagnosed diabetic patients, in which there is a selective optic nerve dysfunction [24], ocular hypertension or glaucoma, patients affected by multiple sclerosis) had an abnormal recovery of the macular function, our evidence could appear in contrast with that of Sadun [25], who states that "the photostress test can be useful in order to separate the maculopathy from the optic neuritis". This contrast could probably be ascribed to different or non-appropriate methodologies being applied to induce the retinal bleaching. In fact, Campos et al. [26], using a different psychophysical evaluation of the visual function (perimetry), observed an abnormal response after exposure to a high luminance level in patients with optic neuritis as well, and these data consistent with the results observed in our multiple sclerosis patients with optic neuritis [21].

Both psychophysical [5] and electrophysiological [3, 4, 15] methods allow us to measure the time needed for macular recovery after an exposure to a bleaching light. With respect to the psychophysical method, VEP recordings allow for a further analysis of the dynamic changes that photostress may induce, with the evaluation of the increase in latency and the decrease in amplitude observed at 20, 40 and 60 s after dazzling.

The VEP recovery to its basal state after photostress, has been related to the resynthesis of photopigment [4]. Since a longer RT was observed in patients with carotid occlusive disease [22, 23], an adequate ocular blood flow

appears to be essential for this process. Furthermore, the process seems not to be exclusively related to the function of outer retina, since the integrity of inner retinal layers may also play a role. This is supported by the evidence that impaired VEP after photostress responses have been observed in patients with ocular hypertension or glaucoma [15, 20], diabetes [16–19], and multiple sclerosis [21]. In these patients, studies performed using Focal-ERG revealed that, at least in their early stages, there is a selective impairment of the inner layers of the central retina [27–30].

It should be noted that the use of natural pupils during the VEP recordings, before and after bleaching, seems to introduce a potential methodological bias. In fact, when patients with afferent pupillary defects are tested, the pupil diameter could not be constricted as much as normal eyes during photostress and this could induce different VEP responses (i.e., P100 delay [31]) in patients and controls. However, in our studies [15–21], due to the high exposure light used, the post-bleach pupillary changes did not differ significantly between patients with maculopathies, diabetes, glaucoma or optic nerve diseases, and their age-matched controls. Therefore this potential methodological bias must be considered only when a different degree of miosis after photostress is observed in the patients tested, with respect to their age-matched controls.

In conclusion, the VEP after photostress represents an objective, although not specific, index of the dynamic properties of macular performance after exposure to intense light stimulation. The combined use of VEP after photostress and Focal-ERG appears to be promising for gaining further insights into the diagnosis and pathophysiology of macular dysfunction, present in several pathologies.

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